INDEX NUMBER

VOL. 49 JUNE, 1955 No. 6

AMERICAN HEART JOURNAL

AN INTERNATIONAL PUBLICATION FOR THE STUDY OF THE CIRCULATION

Contents on Inside Cover

American Heart Journal

CONTENTS FOR JUNE, 1955

Original Communications

Book Reviews

Index

Vol. 49, No. 6, June, 1955. American Heart Journal is published monthly, by The C. V. Mosby Company, 3207 Washington Avenue, St. Louis 3, Missouri, entered as second class matter January 23, 1917 at the Post Office at St. Louis, Missouri, under the Act of March 3, 1879. Additional entry authorized at Jefferson City, Missouri. Subscription Price: United States, and its Possessions, per year $12.00; Canada $13.00; Foreign $13.50. Printed in the U. S. A.

American Heart Journal

VOL. 49 JUNE, 1955 No. 6

Original Communications

BLOOD VOLUME AND RESIDUAL VOLUME OF THE HEART IN DECOMPENSATION

GUSTAV NYLIN, M.D.

STOCKHOLM, SWEDEN

WHEN in 1915, Keith and associates[1] in the United States introduced the dye method using vital red for determination of plasma and blood volume, they opened up a field for research in circulatory studies that has proved extremely fruitful. During the 40 years that have elapsed since then, an extremely comprehensive literature has accumulated on circulatory blood volume and its changes in physiological and clinical conditions. Many conflicting results have been achieved, owing primarily to the kind of test substance to be injected, whether bound to the plasma or the erythrocytes. Among plasma indicators it was an advance when in 1920, Dawson and co-workers[2] selected the blue azo dye (T-1824) as the best one available among sixty different dyes. Until the last few years this indicator has formed the basis for the comprehensive research work about plasma volume which has been done by many investigators, especially by Gibson and Evans,[3] Gregersen,[4] and many others. The total circulatory blood volume has been calculated with the help of plasma volume and hematocrit. There have been conflicting results among many investigators as to the validity of the blue azo dye technique in determination of plasma volume. The most important objection to this method has been that the injected dye (T-1824), even though highly molecular and bound to serum albumin, diffuses into the tissues being absorbed by the endothelial system, passes to the lymph, and so on. As a consequence of this it is difficult to say when mixing between the injected test substance and the circulating blood has taken place. The loss of dye, for example, one hour after injection, varies considerably with different investigators. I think Gregersen's[4] justification of the blue azo dye method deserves great respect.

To some degree it was a great advance when cell-tagging methods by radioactive isotopes were introduced, first by Hahn and associates[5] in 1938. They

Presented in New York Academy of Medicine, September, 1954.
Received for publication Oct. 27, 1954.

used radioactive iron in animal experiments. This method was advanced especially by Peacock and co-workers.[6] The drawbacks of this method were first, the necessity of having a donor, and second, the long half life of the radioactive iron. On the basis of reviewed studies concerning the uptake of radiophosphorus in blood corpuscles, Hevesy and Zerahn[7] in 1942 presented a method for determination of the circulatory red cell volume in rabbits. Some years later

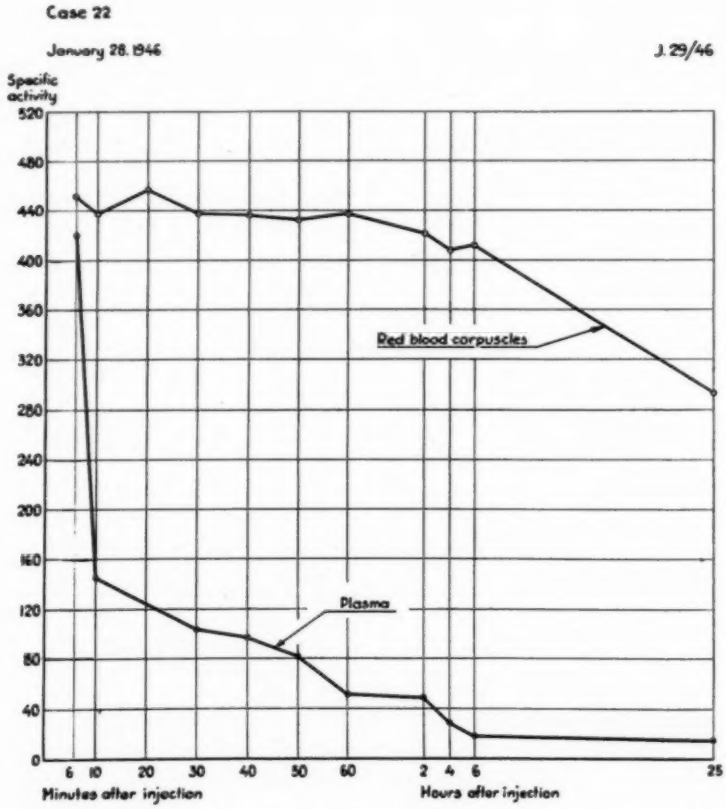


Fig. 1.—Specific activity of red blood corpuscles and plasma during 24 hours after intravenous injection of tagged erythrocytes and plasma. From Nylin, G., and Hedlund, S.: Am. Heart J. **33**:777, 1947.

Hevesy and Nylin tried the method in this clinic. The advantage of this method was that the half life for P^{32} is rather short (14.3 days) and that it is possible to label the patient's red cells in vitro and then inject them intravenously in the patient. Characteristic and important is the fact that the injected red cells retain their activity nearly constant one-half to one hour after injection and lose activity after an hour within the error for the method (Fig. 1). If the labeled red cells are centrifuged free from active plasma, then washed free from active plasma with unlabeled plasma, and then injected, the loss after one hour is higher, up to 8 per cent, but one cannot be sure that through this procedure some hemolysis may not occur (Fig. 2). Since 1942, Nylin and collaborators[8] have used this method in circulatory studies both from a physiological point of view and in clinical conditions. Together with Hevesy, Nylin has used

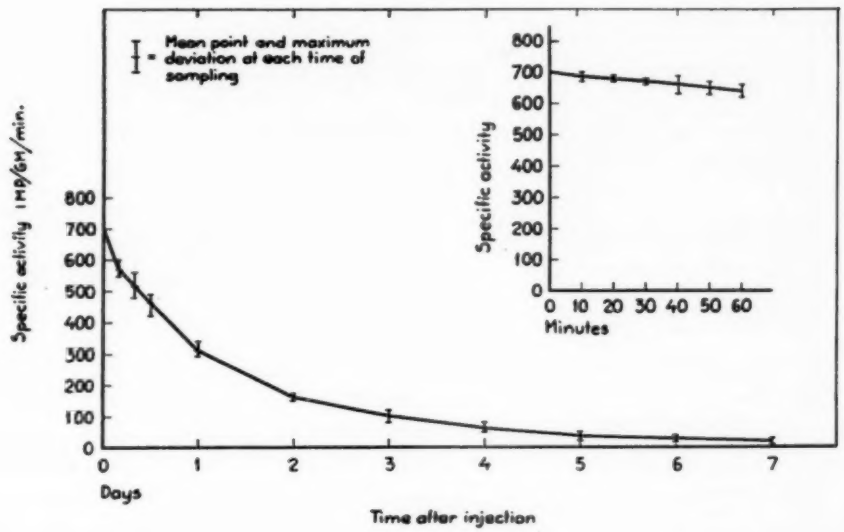


Fig. 2.—Mean rate of fall of corpuscular activity after injection of washed activated red cells (ten experiments).

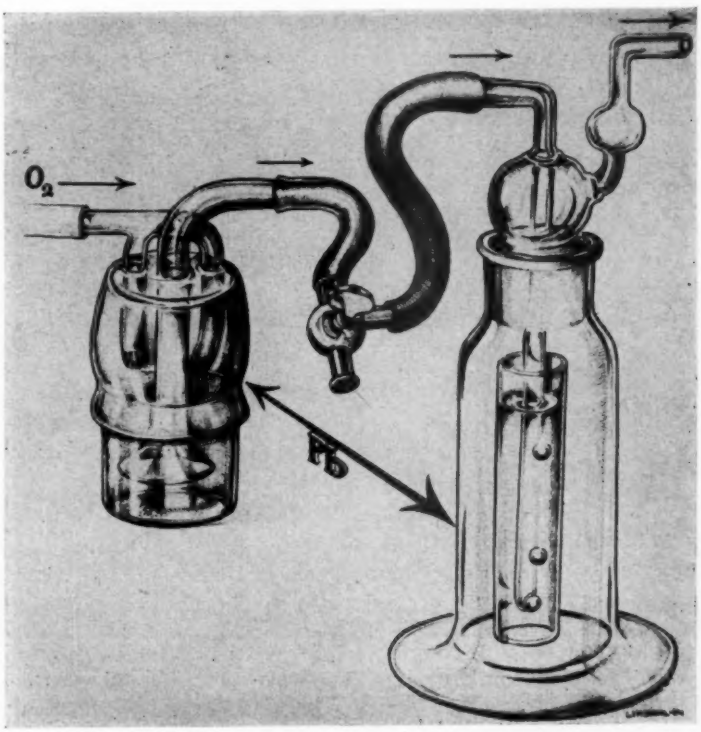


Fig. 3.—Apparatus for labeling the blood with thorium B.

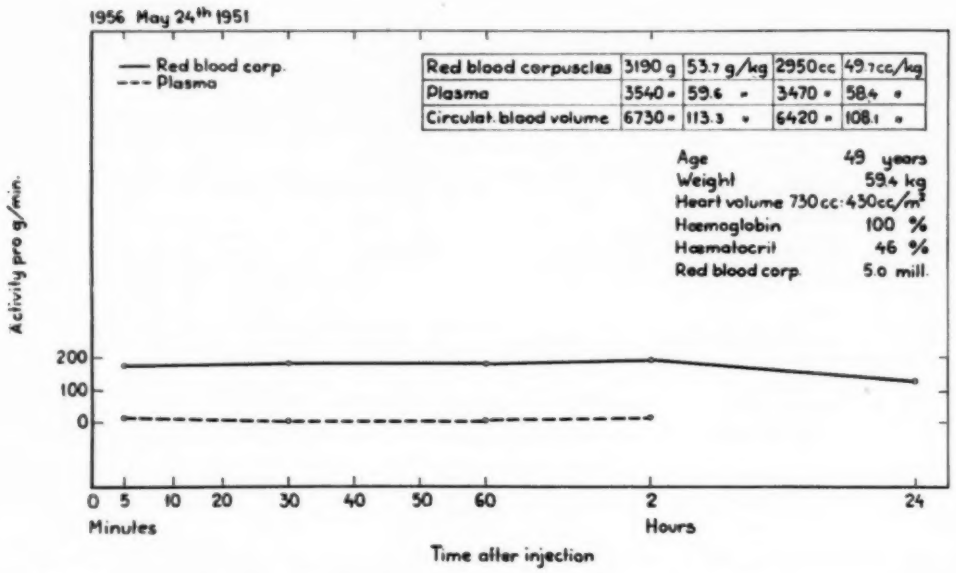


Fig. 4.—Intravenous injection of whole blood labeled with thorium B in a case of cardiosclerosis.

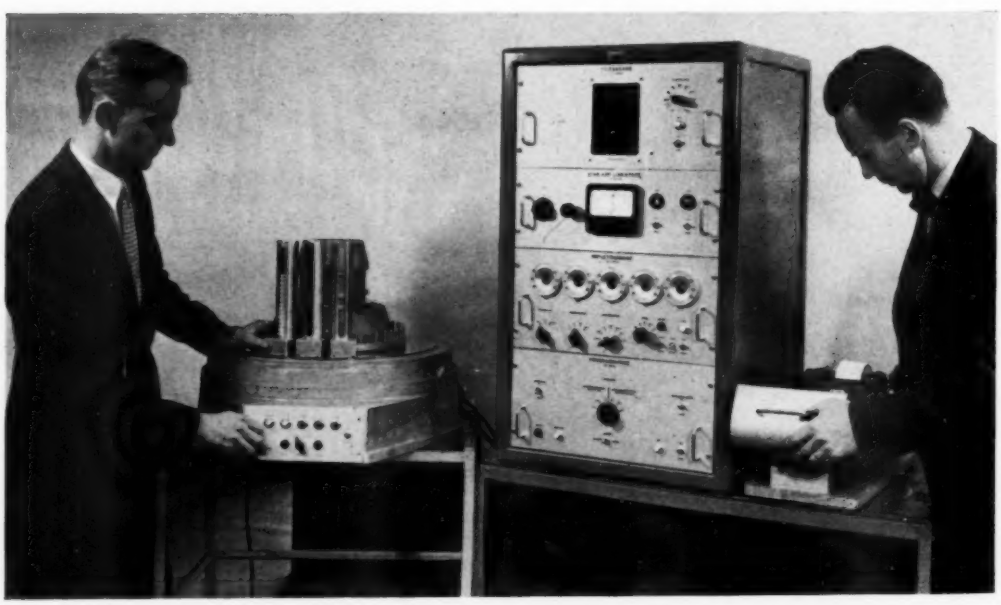


Fig. 5.—The LKB-robot scaler. To the left the sample changer for 425 samples with the Geiger counter in the center. In the middle the robot scaler and to the right the typewriter which inscribes the number of the sample, the counts, and the time for counting.

other isotopes also for labeling the erythrocytes. Thus we have applied K^{42} labeled red cells in blood volume determinations.[9] K^{42} has a very short half life of 12 hours and the loss of activity of injected washed red cells is only 3.5 per cent in one hour. A further improvement of the labeling technique was the introduction of thorium B (Fig. 3).[10] By leading thorium emanation through a blood sample from the patient for 10 to 20 minutes, thorium B, a disintegration product of thoron with a short half life of 10.6 hours, penetrates the red cells, leaving only a negligible amount, under 1 per cent, in the plasma. Thorium B stays for a longer time in the erythrocytes than K^{42} and P^{32}, and the loss within one hour is negligible. As an example, Fig. 4 shows that the activity remains constant for at least two hours after injection and that the loss in 24 hours is about 25 per cent. The other important advantage is that the samples drawn do not have to be centrifuged free from plasma and can be measured on their activity either in cuvettes or after drying on a blotting paper. In cooperation with LKB-Products in Stockholm, a new equipment for counting activity in many blood samples has been constructed, the automatic Robot Scaler, Fig. 5.

Further new radioactive isotopes have recently been introduced in the United States for labeling the erythrocytes. Gray and Sterling[15] have introduced a new method for labeling the red cells with radioactive chromium with a half life of 26.5 days. This new technique shows that the red cells will be constantly labeled up to 24 hours after injection. There is much to support the view that the active labeling technique of especially the red blood cells has further secured the technique in determining the quantity of circulating red blood cells and thereby also the total blood volume. It is also with this method in view that I shall put forward recent results regarding the blood volume in cardiac decompensation. In the last 10 years we have specially concentrated on studying these conditions both with P^{32} and with the thorium B technique. The latest results have been presented in a comprehensive publication by my collaborator, Hedlund.[11] All determinations in the latter work have been carried out with P^{32} labeled whole blood, injected intravenously. The material covers fifty-five cases of cardiac decompensation, thirty-eight men and seventeen women divided into two main groups: vascular heart diseases and valvular heart diseases. From Table I it is seen that, generally speaking, the red cell volume, totally as well as calculated per square meter of body surface, is higher in decompensated then in control cases, higher in decompensated than in compensated cases, higher in men than in women, and higher in valvular than in vascular heart affections. In all groups (Table II) an analysis will show a significant difference between the decompensated and the control cases. Likewise, an almost significant difference between decompensated and compensated cases can be ascertained in total red cell volume in men with vascular heart affections and in women with valvular defects. In the two other groups, no significant differences are traceable, but the material is relatively small. The duration of the cardiac congestion varies from $3\frac{1}{2}$ to 12 years. From Fig. 6 in the group with valvular heart disease it can be seen that the total red cell volume in cubic centimeters per square meter of body surface seems to be almost normal when the insufficiency is of fairly short duration, but gradually increases with the duration of decompensation.

TABLE I. TOTAL VOLUME OF ERYTHROCYTES IN DECOMPENSATED AND COMPENSATED HEART FAILURE AS WELL AS IN CONTROL CASES*

		TOTAL AMOUNT OF ERYTHROCYTES (C.C.)			AMOUNT OF ERYTHROCYTES/BODY SURFACE (C.C./M.²)		
		DECOMPENSATED	COMPENSATED	CONTROL	DECOMPENSATED	COMPENSATED	CONTROL
Males:	Vascular heart diseases	2444 ± 84 461 (30)	2164 ± 70 337 (23)	2166 ± 56 331 (35)	1330 ± 47 258 (30)	1191 ± 42 201 (23)	1131 ± 22 131 (35)
	Valvular heart diseases	2721 ± 282 797 (8)	2662 ± 316 546 (3)		1517 ± 132 373 (8)	1421 ± 158 274 (3)	
Females:	Vascular heart diseases	1783 ± 74 196 (7)	1595 ± 186 416 (5)	1460 ± 103 274 (7)	1119 ± 43 113 (7)	983 ± 114 255 (5)	868 ± 44 115 (7)
	Valvular heart diseases	2119 ± 185 585 (10)	1715 ± 100 245 (6)		1345 ± 114 360 (10)	1042 ± 56 137 (6)	

$\bar{x} \pm s_{\bar{x}}$ = mean ± error of mean
s (n) = standard deviation (number of cases)
*From Hedlund, S.,[11] p. 76.

TABLE II. DIFFERENCES IN MEANS† (TOTAL RED CELL VOLUME C.C./M.² BODY SURFACE)

		DECOMP.—NORMAL	DECOMP.—COMP.	COMP.—NORMAL
Vascular heart diseases	males	199 ± 52 3.83*** (65)	139 ± 63 2.21* (53)	60 ± 47 1.28 (58)
	females	251 ± 62 4.05*** (14)	136 ± 122 1.11 (12)	115 ± 122 0.94 (12)
Valvular heart diseases	males	386 ± 134 2.88** (43)	96 ± 206 0.47 (11)	290 ± 160 1.81 (38)
	females	477 ± 122 3.91** (17)	303 ± 127 2.39* (16)	174 ± 71 2.45* (13)
		VALVULAR—VASCULAR HEART DISEASE		MALES—FEMALES
Decomp.	males	187 ± 140 1.3 (38)	Valvular heart diseases decomp.	172 ± 174 0.99 (18)
Decomp.	females	226 ± 122 1.85 (17)	Vascular heart diseases decomp.	211 ± 64 3.3** (37)

$d \pm \varepsilon_d$ = difference ± error of difference

$t \quad (n) = t = \frac{d}{\varepsilon_d}$ (number of cases)

The following intervals of significance have been used (Cramér, 1946): $p > 0.05$ not significant

*$0.05 \geq p > 0.01$ almost significant

**$0.01 \geqq p > 0.001$ significant

***$0.001 \geqq p$ highly significant

†From Hedlund, S.,[11] p. 77.

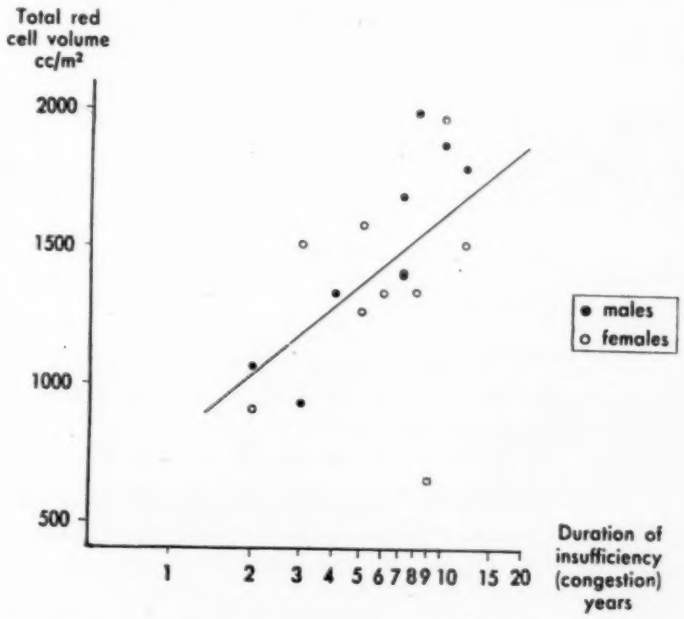


Fig. 6.—Relationship between duration of congestion and total red cell volume in valvular diseases. From Hedlund, S.,[11] p. 82.

There seems to be a certain correlation between red cell volume and the degree of decompensation evaluated by the degree of edema and venous pressure. In this material the total heart volume showed pronounced enlargement, to several times the normal size, Table III. In the control material there is a significant correlation between heart volume and total red cell volume, and in the material

TABLE III. HEART VOLUME IN CONGESTIVE HEART FAILURE AS WELL AS IN NORMAL CASES*

	MALES	FEMALES
Vascular heart diseases	1832 ± 105 483 (21)	1353 ± 116 201 (3)
Valvular heart diseases	2542 ± 246 697 (8)	1924 ± 204 579 (8)
Normal cases according to Nylin	740 ± 9 134 (240)	571 ± 7 97 (181)

$\bar{x} \pm \varepsilon_{\bar{x}}$ = mean ± error of mean

s (n) = standard deviation (number of cases)

*From Hedlund, S.,[11] p. 82.

of cardio-decompensation a tendency toward greater red cell volume in pronounced heart dilatation. It has been of special interest to follow the changes in red cell volume during treatment of the congestion. From Table IV it is seen that in those cases that have improved there is a highly significant decrease in red cell volume, especially in men.

TABLE IV. CHANGES IN TOTAL VOLUME OF ERYTHROCYTES AFTER TREATMENT OF CONGESTIVE HEART FAILURE*

	IMPROVED	SLIGHTLY IMPROVED AND UNIMPROVED
Males	−379 ± 84 4.51*** (20)	109 ± 145 0.75 (5)
Females	−459 ± 161 2.85* (9)	267 ± 454 0.59 (2)

$d = \varepsilon_d$ = difference ± error of difference

t $(n) = t = \frac{d}{\varepsilon_d}$ (number of cases)

*From Hedlund, S.,[11] p. 82.

For explanation of symbols see Table II.

The plasma volume has been determined in decompensated and compensated cases in this material and a highly significant increase has been found among the decompensated. The plasma volume has been determined with the blue azo dye method.

The pathogenesis of the increase of red cell volume coordinated with congestion has been the subject of comprehensive investigations by my assistant

Dr. Hedlund concerning the erythropoiesis during the stage of decompensation and the changes in the hematologic process, during and after a treatment that leads to compensation. The following results have been achieved.

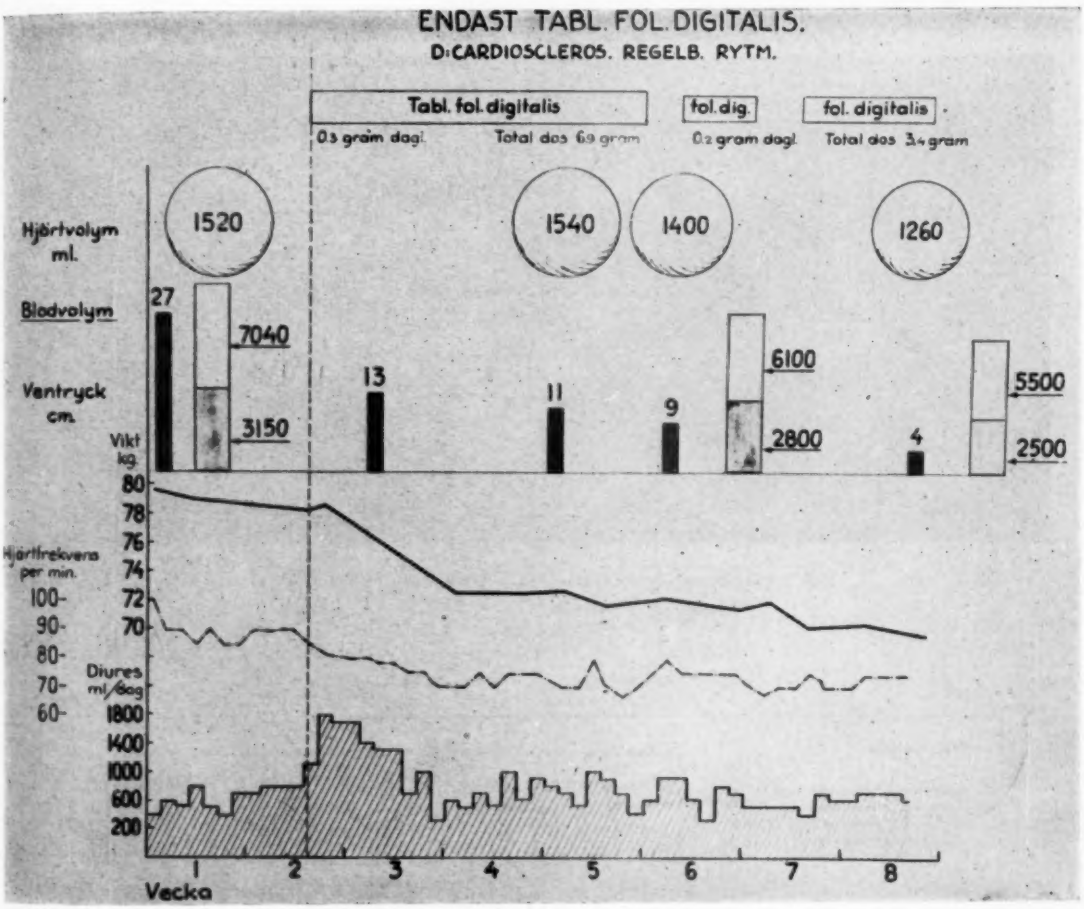


Fig. 7.—The effect of treatment with only digitalis on red cell volume, total blood volume, venous pressure, heart volume, pulse rate, and diuresis in a case of decompensation.

In decompensation, the bone marrow shows a comparatively greater percentage of nucleated red blood corpuscles than normal. Apparently this increase corresponds, numerically, to a recorded increase of the orthochromatic erythroblasts. A correlation has been ascertained between the number of nucleated red blood corpuscles and the arterial oxygen saturation. Very possibly it is the anoxia, together with some endocrine factor, that elicits the polycythemic reaction, and there is a correlation between oxygen saturation and the reticulocytosis. There occurs, too, an iron deficit, and the mean corpuscle diameter of the red cells is elevated. The macrocytes seem to have a central hematopoetic genesis which is supported by animal experiments of Plum and Hedlund.[12]

The changes in the hematologic process during treatment that leads to compensation have been studied. The erythropoetic activities are diminished, a fact reflected in the reticulocyte curve. Probably, a population of macrocytes, with a supposedly shorter lease of life than normal, disappears from the circulation. It is in this light that the increase in serum iron must be viewed.

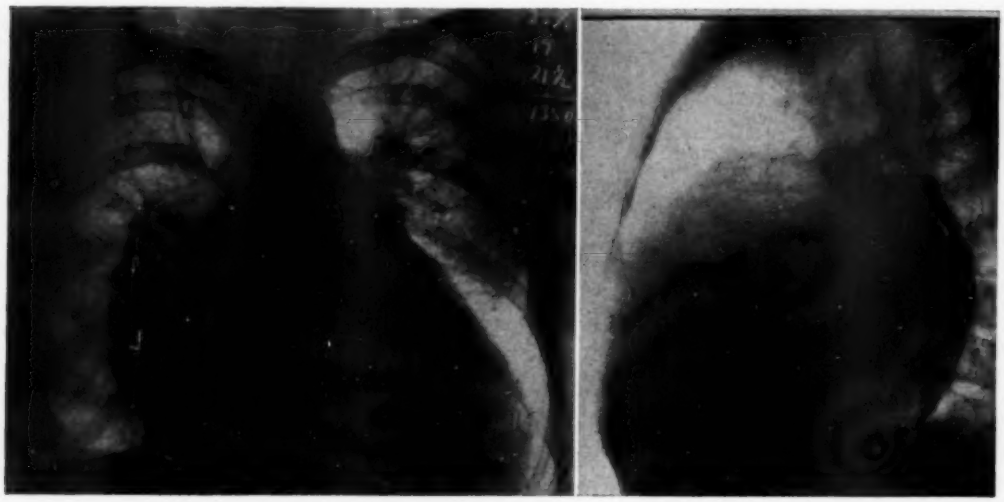


Fig. 8.—Extreme heart dilatation. Heart volume 4,350 c.c.

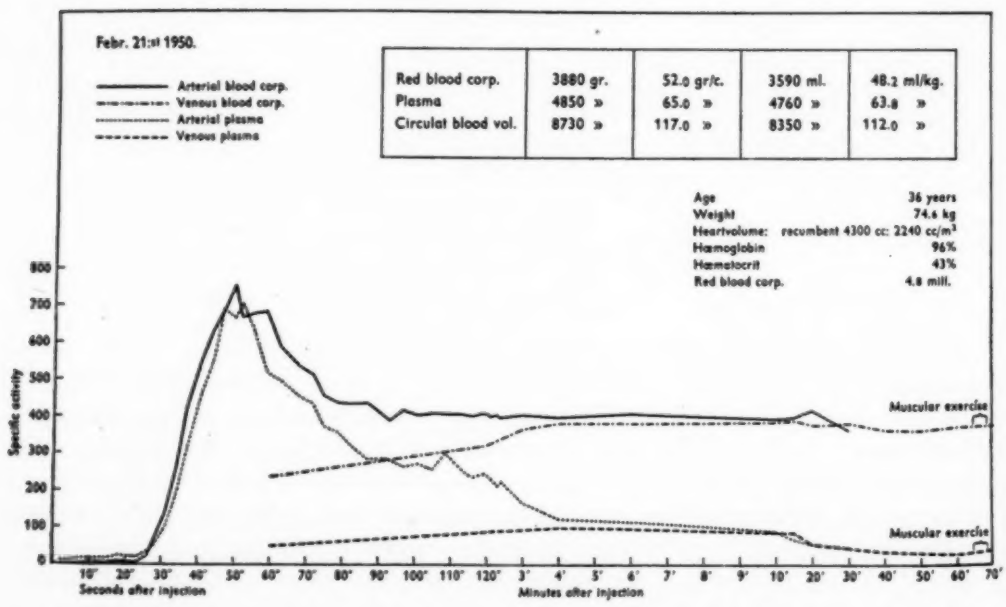


Fig. 9.—Dilution curve of labeled red blood corpuscles and plasma for both arterial and venous blood in a case of severe heart dilatation. Same case as Fig. 8.

We are convinced by our studies that the red cell volume in general is increased in cardiac decompensation and that the increase is greater when the decompensation has lasted longer. As an example of pronounced increase of red cell volume I will describe the following case, where the patient had decompensated cardiosclerosis with moderate cardiac enlargement (Fig. 7). The heart volume amounted to 1,520 c.c. The venous pressure when the patient was admitted to the clinic was very high, 27 cm., the body weight 80 kilograms. The heart rate was rapid, 100/min., but there was still sinus rhythm. The red cell volume before starting treatment with only digitalis amounted to 3,150 grams or 40 grams per kilogram, which is a very high value. The effect of only digitalis treatment resulted in a decrease of venous pressure, the loss of 10 kilograms of body weight, a decrease in pulse rate, and above all reduced heart volume of 260 c.c. and a decrease of red cells by 650 grams in two months. I have collected ten cases, most of them with extreme heart dilatation, where the red cell volume and the total blood volume have been determined (Table V). Almost parallel with the decreasing red cell volume from 3,810 c.c. in No. 1 to 2,410 in No. 10, there is a decrease in heart volume from 3,050 c.c. to 1,520 c.c., respectively. The biggest heart I have seen, No. 4, with a heart volume of 4,300 c.c. i.e. 2,240 c.c./M^2 (the upper limit for the normal is 500 c.c./M^2), has been ex-

TABLE V. CORRELATION BETWEEN RED CELL VOLUME AND HEART VOLUME IN TEN CASES WITH BIG HEARTS

CASE NO.	RED CELL VOLUME (C.C.)	C.C./KG.	HEART VOLUME (C.C.)	TOTAL BLOOD VOLUME (C.C.)	C.C./KG.	WEIGHT (KG.)
1.	3810	55	3050	8560	122	70
2.	3280	52	4160	7540	119	63
3.	2780	49	3760	6640	116	57
4.	3590	48	4300	8350	112	75
5.	3400	43	2560	8080	103	79
6.	2481	42	3300	6616	113	59
7.	2820	40	1800	6265	88	71
8.	2185	38	1530	5205	91	58
9.	2120	35	1080	5370	90	60
10.	2410	33	1520	5670	78	73

amined in detail. Figs. 8 and 9 show a total blood volume of 8,350 c.c., which is about the double the normal. Even the red cells are about twice the normal 3,880 grams or 52 grams per kilogram. It is highly probable that a great part of the enormous increase of red cells and total blood volume is stored in the heart itself and in the heart cavities as an increased amount of residual blood. Probably the extremely dilated heart in this case contains more than 2 liters of blood. With the help of the dilution curve from brachial arterial blood after intravenous injection of radioactively labeled red cells it is in some cases possible to calculate both the minute volume of the heart and the thoracic pool, i.e., the amount of blood in the heart and lungs together. In this case it was impossible to make these calculations, but on the other hand the type of the dilution curve differs

greatly from the normal. The labeled cells appear extremely late in the arterial blood and the decline from the maximum is very retarded and reaches the constant level late. The whole curve is shifted over to the right in contrast to the normal curve. All this speaks in favor of the assumption that the residual blood of the heart must be very large. Our studies about the quantity of the residual blood of the heart were furthered in the beginning by our heart volume studies. Therefore, a short description of our method for determination of the

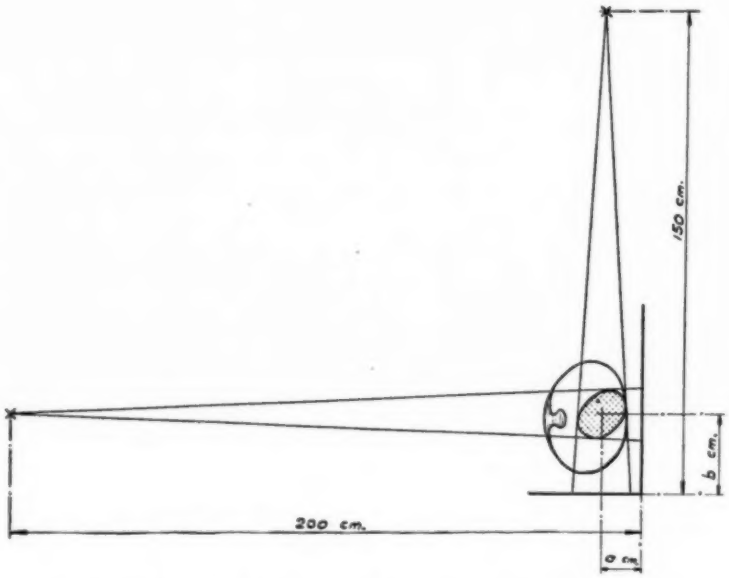


Fig. 10.—Biplane radiography for heart volume determination.

roentgenologic heart volume should be given. Over 20 years ago Lysholm, Nylin, and Quarnå, and later Liljestrand, Lysholm, Nylin, and Zachrisson,[13] introduced the method for heart volume determination now commonly used in Sweden. The roentgenograms are taken in frontal projection 2 mm. from the patient, and the sagittal at a distance of 1.5 mm. This so-called biplane radiography (Fig. 10) makes it possible to calculate the heart volume,

$$V = 0.38 \times l \times m \times n$$

where l denotes length, m breadth of heart silhouette in frontal projection, and n the diameter in sagittal projection. The normal heart volume varies between 250 and 500 c.c./M.^{2} of body surface. One of my assistants, Dr. Friedman, has made a comprehensive study of the validity of this method.[14] He has carried out biplane radiography ante- and post-mortem and shown that following rigor mortis the heart decreases in volume about 30 per cent. Furthermore, he has found exceptionally good agreement between post-mortem x-ray heart volume and the displacement volume of the removed heart (Fig. 11). We in Sweden are of the opinion that this method for heart volume determination, which has now been used as a routine method for over 20 years, gives us important information about our cardiac patients. In particular, this method has informed us about the changes of the amount of the residual blood in the

heart. Probably the normal heart contains a few hundred cubic centimeters of residual blood. In clinical conditions there must be pronounced changes in this amount, especially in cardiac decompensation. As an example of pronounced change during treatment of a case of heart dilatation that to some

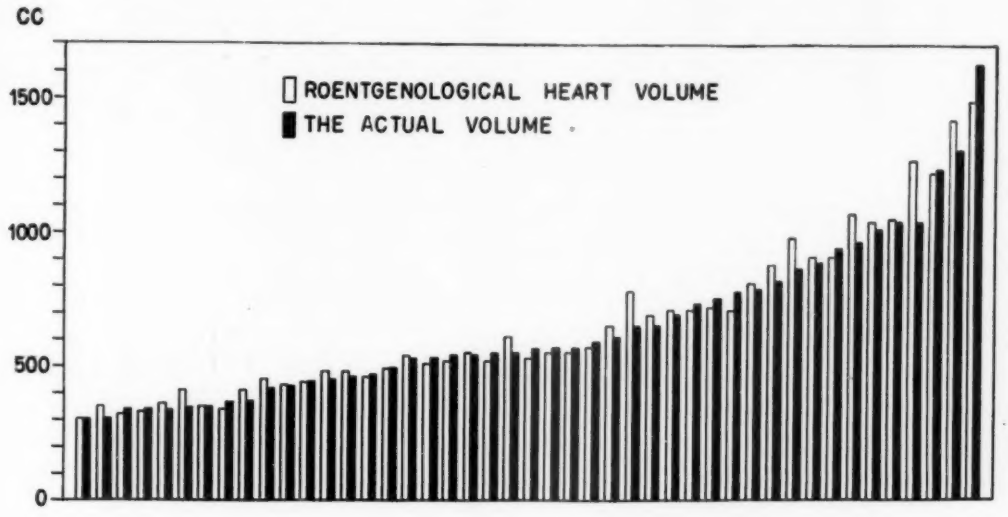


Fig. 11.—Comparison between roentgenologic heart volumes after death and water displacement of the removed hearts (45 cases). From Friedman, C. E.,[14] p. 38.

degree is reversible, I should like to mention the following case. Fig. 12 illustrates a decrease of heart volume by 1,200 c.c. This method cannot show the amount of residual blood in the heart, but indirectly we are able to show that in clinical conditions with cardiac decompensation this amount must be of hitherto unknown magnitude. It is highly probable that it is the great amount of residual blood that is mainly responsible for the pronounced increase in red cell volume in cardiac decompensation. As an example of the approximate calculation of this amount, from the dilution curve with radioactively labeled erythrocytes (Fig. 13) one can calculate the minute volume of the heart and also the blood content in the chest (the heart and lungs) and in this case the thoracic pool amounts to 2.9 liters (Case 1, Table VI), where the amount of the residual blood in the heart amounts approximately to about 2,000 c.c. The ante- and postmortem heart volume determinations, together with control of the latter with displacement method, show that in this case with a heart volume during life of 3,050 c.c. the residual blood can be estimated at 2,000 c.c. (Table VII). In this case the amount of red cells was very high, 4,120 grams or 59 grams per kilogram which is twice the normal. With the introduction of the catheterization technique it has been possible to obtain through a catheter in the pulmonary artery and through a catheter in the brachial artery simultaneous dilution curves from the right and the left heart. It has not been possible to get enough information about normal cases. We think we have no indication for doing

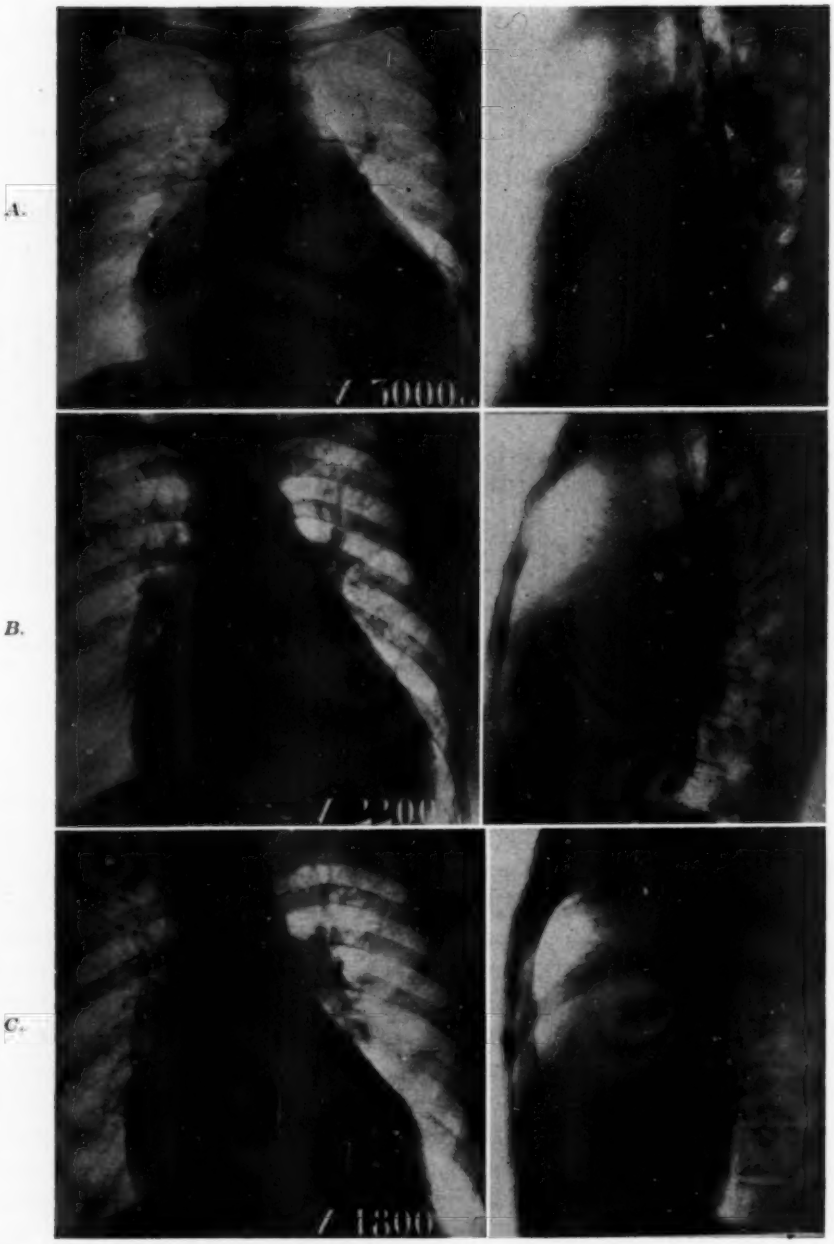


Fig. 12.—Decrease in heart volume following treatment. *A*, May 26, 1936. *B*, June 11, 1936. *C*, June 22, 1936.

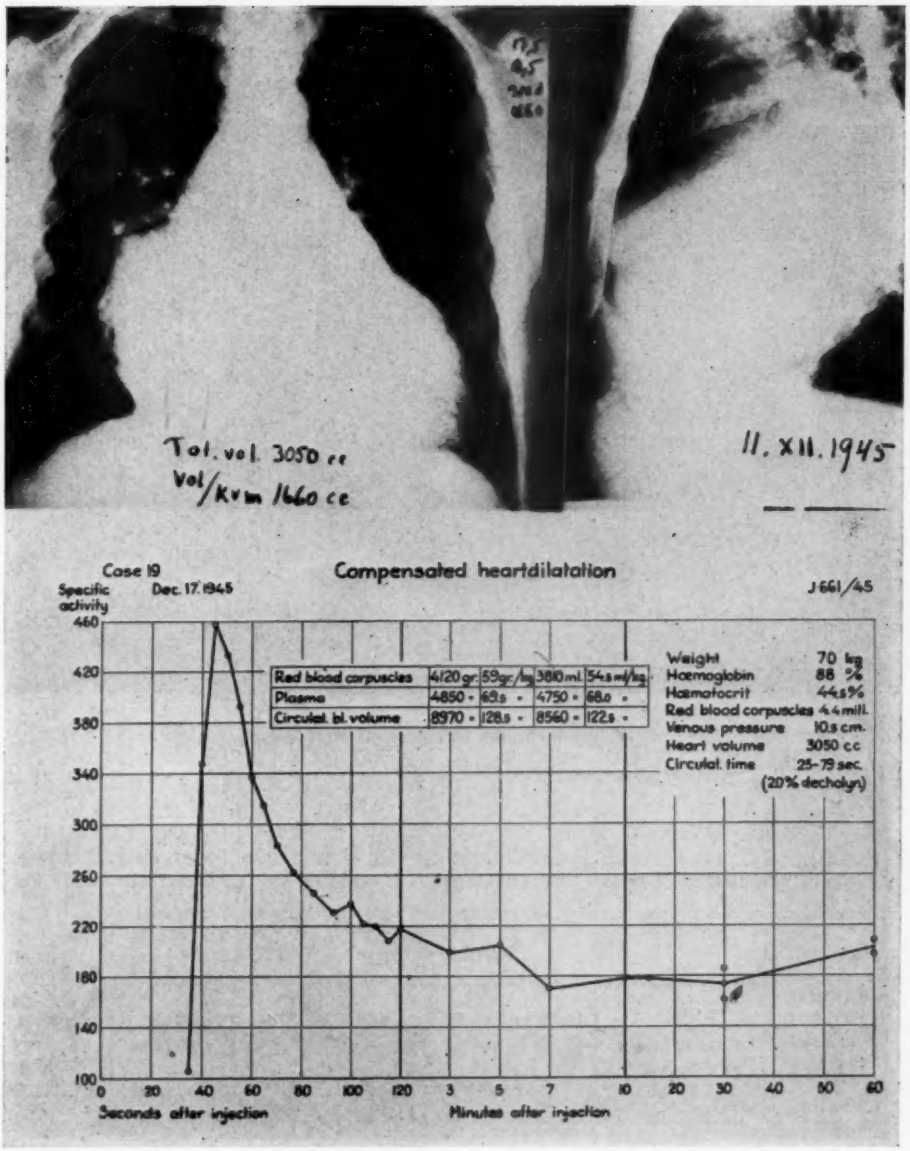


Fig. 13.—Dilution curve from the arterial blood after intravenous injection of P^{32} labeled blood in a case of heart dilatation. From Nylin, G., and Hedlund, S.: Am. Heart J. **33**:776, 1947.

catheterization in normals. On the other hand, I have a case of operated coarctation with normal heart volume where indication for control catheterization was present. In this case (Figs. 14 and 15) dilution curves were obtained which show the very rapid circulation, with a maximum for the activity of the injected red cells in the pulmonary artery a few seconds earlier than for the same in the brachial arterv.

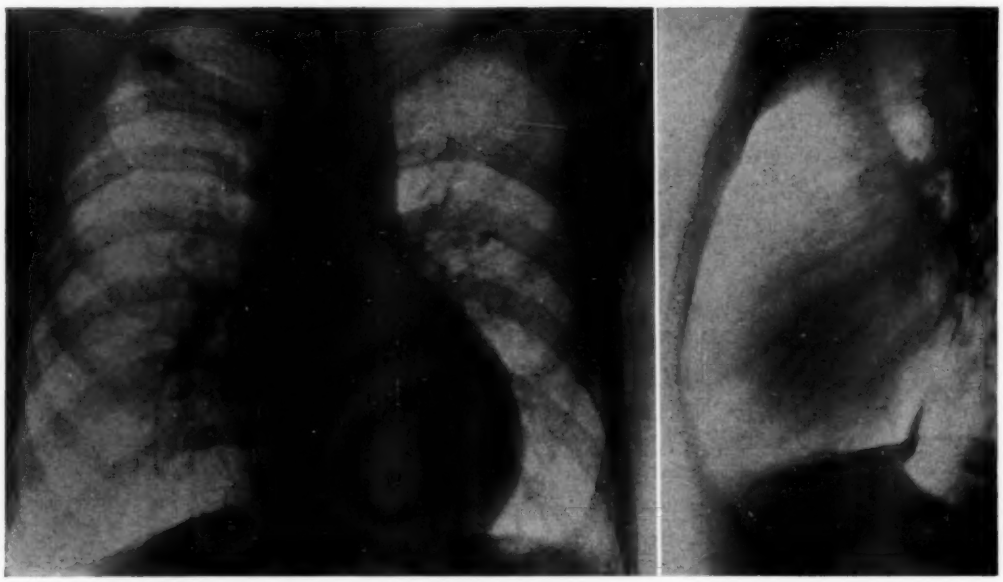


Fig. 14.—Normal heart volume in a case of operated coarctation.

TABLE VI. CARDIAC OUTPUT, POOL VOLUME OF THE CHEST AND TOTAL CIRCULATORY BLOOD VOLUME IN NORMAL SUBJECTS AND IN PATIENTS WITH HEART DISEASE*

CASE	CARDIAC OUTPUT (X_1) (LITERS)	POOL VOLUME				TOTAL BLOOD VOLUME IN THE BODY (V_t) (LITERS)
		UPPER LIMIT ($V_1 = X_1 \Delta t$) (LITERS)	LOWER LIMIT ($V_2 = \frac{X_1}{\lambda}$) (LITERS)	MEAN VALUE ($V_0 = \frac{V_1 + V_2}{2}$) (LITERS)	% OF TOTAL BLOOD VOLUME	
1	3.7	2.9	2.8	2.85	33	8.6
2	4.4	2.2	1.3	1.75	32	5.5
3	5.0	1.9	1.2	1.55	34	4.5
4	2.3	1.3	1.1	1.20	29	4.2
5	1.35K	0.45K	0.15K	0.30K	30	K
6	1.60K	0.41K	0.29K	0.35K	35	K
7	0.79K	0.42K	0.21K	0.32K	32	K
8	1.10K	0.43K	0.17K	0.30K	30	K

*From Nylin, G., and Celander, H.: Determination of Blood Volume in the Heart and Lungs and the Cardiac Output Through the Injection of Radiophosphorus, Circulation **1**:80, 1950.

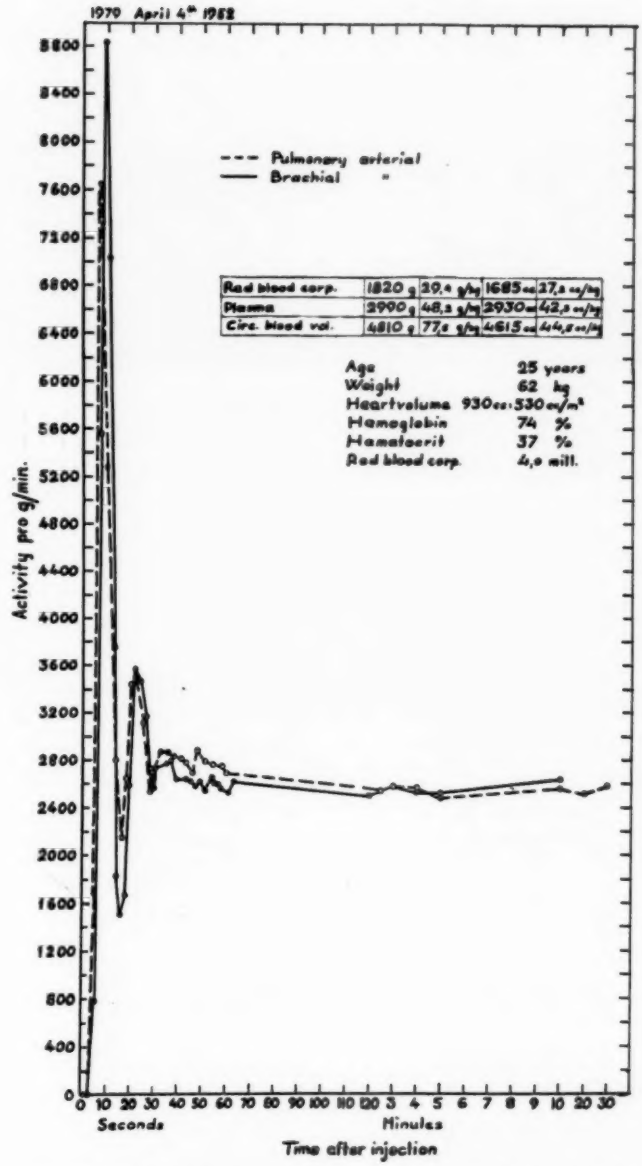


Fig. 15.—Dilution curves of labeled erythrocytes in pulmonary and brachial arterial blood after intravenous injection of labeled blood in a case of operative coarctation.

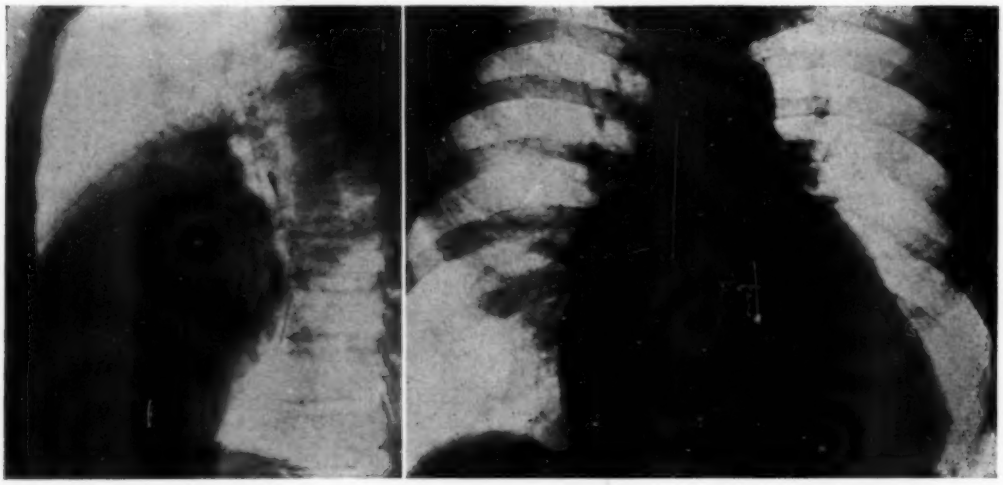


Fig. 16.—Heart volume in a case of heart dilatation.

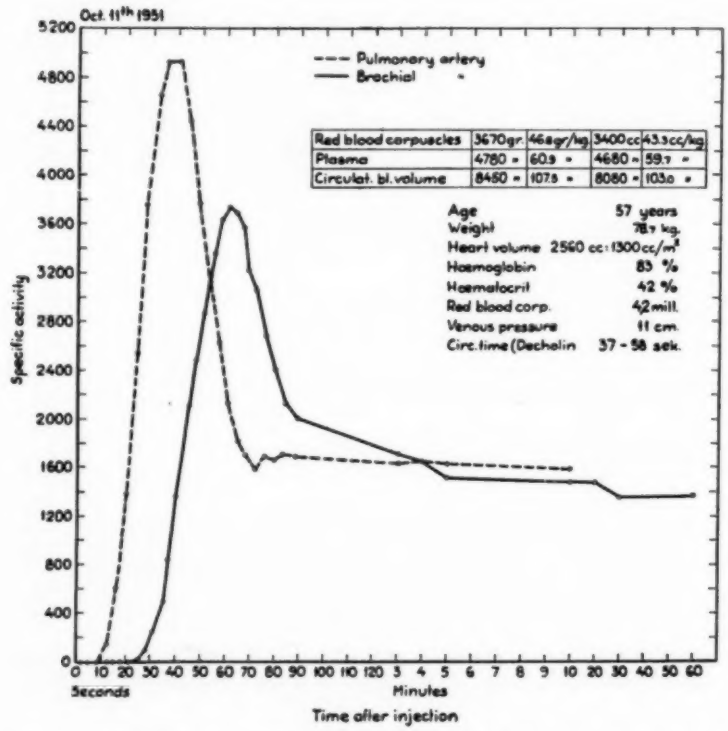


Fig. 17.—Dilution curves in pulmonary and brachial arterial blood after intravenous injection of labeled blood in a case of heart dilatation.

TABLE VII

X-Ray heart volume	ante-mortem	3050 c.c.
X-Ray heart volume	post-mortem	2200 c.c.?
Displacement volume	post-mortem	2100 c.c.
Residual blood	post-mortem	1050 c.c.
Heart muscle volume	post-mortem	930 c.c.
Heart muscle weight	post-mortem	970 gram
Residual blood of the heart during life		2000 c.c.
Pool volume of the chest		2900 c.c.
Minute volume of the heart		3700 c.c.
Total blood volume		8600 c.c.

In dilated hearts with a greater amount of residual blood the dilution curves are quite different and both show retarded speed of circulation and are shifted over to the right. Fig. 16 shows the x-ray of the dilated heart with a heart volume of 2,500 c.c., i.e. 1,300 c.c./M^2. We have calculated the minute volume of the heart from both dilution curves, Fig. 17, and obtained exactly the same value, 3.4 liters, which corresponded to the Fick method. The total pool volume of chest amounted to 2.7 liters.

SUMMARY

A method of labeling the red cells with P^{32} and especially with thorium B is described. These methods have been used for determination of the total red cell volume and its changes during treatment of cardiac decompensation. It has been found that the red cell volume is increased during decompensation. Much of the increase in red cell volume is to be referred to increase of the residual blood in the heart. With the help of measuring (x-ray) heart volume and displacement volume of the heart, together with calculation of dilation curves, it is possible to get information about the amount of residual blood in the heart.

SUMMARIO IN INTERLINGUA

Es describite methodos pro etiquettar erythrocytos con P^{32} e specialmente con thorium B. Iste methodos esseva usate pro determinar le volumine total de erythrocytos e su cambiamentos durante le tractamento de decompensation cardiac. Il esseva constatate que le volumine erythrocytic se augmenta in le curso del decompensation. Un grande portion de iste augmento debe esser ascribite a un augmento del sanguine residual intra le corde. Per medio de mesurationes roentgenologic del volumine cardiac e del volumine de displaciamento del corde insimul con calculationes de curvas de dilatation, il es possibile obtener datos in re le quantitate de sanguine residual intra le corde.

REFERENCES

1. Keith, N. M., Rowntree, L. G., and Geragthy, J. T.: A Method for the Determination of Plasma and Blood Volume, Arch. Int. Med. **16**:547, 1915.
2. Dawson, A. B., Evans, H. M., and Whipple, G. H.: Blood Volume Studies. III. Behavior of Large Series of Dyes Introduced Into the Circulating Blood, Am. J. Physiol. **51**:232, 1920.

3. Gibson, J. G., Jr., and Evans, W. A., Jr.: Clinical Studies of the Blood Volume. II. The Relation of Plasma and Total Blood Volume to Venous Pressure, Blood Velocity Rate, Physical Measurements, Age and Sex in Ninety Normal Humans, J. Clin. Invest. **16**:317, 1937.
4. Gregersen, M. I.: A Practical Method for Determination of Blood Volume With the Dye T-1824, J. Lab. & Clin. Med. **29**:1266, 1944.
5. Hahn, P. F., Bale, W. F., Lawrence, E. O., and Whipple, G. H.: Radioactive Iron and Its Metabolism in Anemia, J. A. M. A. **3**:2285, 1938.
6. Peacock, W. C., Evans, R. S., Irvine, J. W., Jr., Good, W. M., Kip, A. F., Weiss, S., and Gibson, J. G., Jr.: Use of 2 Radioactive Isotopes of Iron in Tracer Studies of Erythrocytes, J. Clin. Invest. **25**:605, 1946.
7. Hevesy, G., and Zerahn, K.: Determination of the Red Corpuscle Content, Acta physiol. scandinav. **4**:376, 1942.
8. Nylin, G.: Blood Volume Determinations With Radioactive Phosphorus, Brit. Heart J. **7**:81, 1945.

—— The Dilution Curve of Activity in Arterial Blood After the Injection of Labeled Corpuscles, Am. Heart J. **30**:1, 1945.

—— Studies on the Circulation With the Aid of Blood Corpuscles Labeled With Radioactive Phosphorus Compounds. Arkiv för Kemi, Mineralogi och Geologi. **20** A: nr 17, 1, 1945.

—— The Effect of Adrenalin Injected Intravenously on the Volume of Circulating Erythrocytes, Acta cardiol. **3**:225, 1946.

—— Circulatory Blood Volume of Some Organs, Am. Heart J. **34**:174, 1947.

—— The Effect of Heavy Muscular Work on the Volume of Circulating Red Corpuscles in Man, Am. J. Physiol. **149**:180, 1947.

—— and Biörck, G.: Circulatory Corpuscle and Blood Volume in the Case of Patent Ductus Arteriosus Before and After Ligation, Acta med. scandinav. **127**:434, 1947.

—— and Celander, H.: Determination of Blood Volume in the Heart and Lungs and the Cardiac Output Through the Injections of Radiophosphorus, Circulation **1**:76, 1950.

—— and Hedlund, S.: Weight of Red Blood Corpuscles in Heart Failure Determined With Labeled Erythrocytes During and After Decompensation, Am. Heart J. **33**:770, 1947.

—— and Hedlund, S.: Further Studies of the Circulation With Radioactive Erythrocytes, Am. Heart J. **37**:543, 1949.

—— and Hedlund, S.: Variations on the Quantity of Red Blood Corpuscles in Cases of Heart Failure, Acta med. scandinav., suppl. **206**:112, 1948.

—— and Hedlund, S.: Die Anwendung der Isotopen in der Cardiologie, Berl. med. Ztschr. **1**:217, 1950.

—— and Lavander, M.: Studies of the Circulation With the Aid of Tagged Erythrocytes in a Case of Orthostatic Hypotension (Asympathicotonic Hypotension), Ann. Int. Med. **28**:723, 1948.

—— and Malm, M.: Über die Koncentration von mit Radioaktiven Phosphor markierten Erythrocyten in Arterienblut nach der intravenösen Injektion solcher Blutkörperchen, Cardiologia **7**:153, 1943.

—— and Pannier, R.: L'influence de l'orthostatisme et du chock sur la vitesse circulatoire déterminée a l'aide du phosphore radioactif, Arch. Int. Pharmacodyn. **73**:401, 1947.

—— and Wade, G.: The Loss of Activity From Blood Cells and Plasma Which Have Been Labeled With Radioactive Phosphorus (P^{32}), Ark. f. Kemi **3**:413, 1951.

9. Hevesy, G., and Nylin, G.: Application of ^{42}K Labeled Red Corpuscles in Blood Volume Measurements, Acta physiol. scandinav. **24**:285, 1952.
10. Hevesy, G., and Nylin, G.: Application of "Thorium B" Labeled Red Corpuscles in Blood Volume Studies, Circulation Res. **1**:102, 1953.
11. Hedlund, S.: Studies on Erythropoiesis and Total Red Cell Volume in Congestive Heart Failure, Acta med. scandinav. suppl. 284,**146**: 1953.
12. Plum, C., and Hedlund, S.: Some Investigations on the Importance of the Oxygen Tension to the Diameter of the Blood Corpuscles, With Special Reference to the Change Occurring in the Partial Ligation of the Vena Cava Inferior in Rat, Acta med. scandinav. suppl. 266,**142**:839, 1952.
13. Liljestrand, G., Lysholm, E., Nylin, G., and Zachrisson, G.: The Normal Heart Volume in Man, Am. Heart J. **17**:406, 1939.
14. Friedman, C. E.: Heart Volume, Myocardial Volume, and Total Capacity of the Heart Cavities in Certain Heart Diseases, Acta med. scandinav., suppl. 257,**140**:3, 1951.
15. Gray, S., and Sterling, K.: The Tagging of Red Cells and Plasma Proteins With Radioactive Chromium, J. Clin. Invest. **29**:1604, 1950.

THE RELATIONSHIP BETWEEN RENAL BLOOD FLOW, GLOMERULAR FILTRATION RATE AND SODIUM EXCRETION, CARDIAC OUTPUT AND PULMONARY AND SYSTEMIC BLOOD PRESSURES IN VARIOUS HEART DISORDERS

LARS WERKÖ, M.D., JAN EK, M.D., EDVARDAS VARNAUSKAS, M.D., HÄRJE BUCHT, M.D., BENGT THOMASSON, M.D., AND HARALD ELIASCH, M.D.

STOCKHOLM, SWEDEN

SEVERAL investigators have demonstrated that the renal blood flow and glomerular filtration rate are decreased in congestive heart failure.[1,6,10,11,14-16] Some, however, have observed that the disappearance of the general congestion on treatment may occur without any appreciable change in renal blood flow or filtration rate. It has also been found that patients with mitral valvular disease may have markedly impaired renal circulation believed to be typical of congestive heart failure, long before any signs of such failure have appeared.[20,21]

It is of interest to know to what extent such alterations in renal blood flow can be found not only in mitral valvular disease but also in other cardiovascular disorders before the onset of congestive failure.

It is also important to know in what manner the existence of a heart lesion is mediated to the kidneys. In heart disease, the circulation is modified by increasing blood pressures in the venous systems or by deviation of the arterial pressures from normal with or without alteration in total blood flow (the cardiac output). The relationship between pressures and flow in the pulmonary and systemic circuits, on the one hand, and the renal circulation and function, on the other, should not be established by inference but from results obtained on simultaneous determinations of these items.

The present report deals with a study of the renal circulation and renal function in a large number of patients with various heart or lung diseases, that may give rise to congestive failure. Most observations have been made during rest. In some patients the reactions to exercise or to a rapid infusion of isotonic glucose solution have been studied. The investigations have been performed with a technique allowing the study of the inter-relationship between the pulmonary or systemic circulation and the renal circulation and sodium excretion.

From the IVth Medical Service and Central Laboratory, St. Erik's Hospital, Stockholm, Sweden.

Aided by grants from the Swedish Medical Research Council and the Wallenberg Foundation.

Presented before the Second Scandinavian Meeting for the Study of Renal Function and Disease held in Stockholm, Sweden, May, 1954.

Received for publication Nov. 11, 1954.

MATERIAL

One hundred forty-six patients with various heart disorders were studied. They consisted of thirty-four patients with congenital heart disease: ten patients with auricular septal defect, twelve patients with patent ductus arteriosus, four patients with Eisenmenger's complex, five patients with coarctation of the aortas, and three patients with congenital dilatation of the pulmonary arch. There were seven patients with primary pulmonary disease: five with emphysema or fibrosis and two with "primary pulmonary hypertension." There were four patients with constrictive pericarditis, two patients with polycytemia, and fifteen patients with hypertensive cardiovascular disease. In addition, twelve patients with aortic valvular disease and seventy-two patients with mitral valvular disease, predominantly stenosis, were also investigated.

The patients with auricular septal defect and those with patent ductus were divided into two groups: one with normal and one with elevated pressure in the pulmonary artery (mean pressure above 20 mm. Hg). Clinical signs of congestive heart failure were observed only in those patients with constrictive pericarditis and in some with mitral valvular disease.

The patients with aortic and mitral valvular disease were divided into groups after their functional capacity according to the New York Heart Association.[17] Those in congestive failure were placed in a separate group.

The details of clinical findings in relation to the physiological measurements will not be considered in this report.

METHOD

All studies were performed in the morning with the subjects recumbent and in the postabsorptive state, except for one-half liter of plain water given perorally before the start of the procedure.

The pulmonary artery was catheterized according to Cournand[5,12,13] and an indwelling arterial needle placed in the brachial artery. Cardiac output was determined according to the direct Fick principle with simultaneous sampling of blood from the pulmonary and brachial arteries and expired air. The blood gases were determined on a Van Slyke apparatus and the air gases on a Haldane apparatus. Blood pressures in the pulmonary and systemic circuit were registered with Tybjaerg-Hansen electrical capacitance manometers.[19]

Resting values for cardiac output and blood pressures were obtained after more than one-half an hour's rest after the catheter had been placed in the pulmonary artery.

The renal clearances for inulin, endogenous creatinine, and para-aminohippurate were determined simultaneously, in some patients after a single intravenous injection of inulin and a single intramuscular injection of para-aminohippurate.[4] In other patients, these substances were given intravenously with a constant-speed injection syringe. Urine was collected at 10 to 15 minute intervals through an indwelling catheter, and the bladder was rinsed twice with distilled water and air after each urine collection. Resting clearance values were obtained during two to three periods. The last resting clearance period was always completed shortly after the determination of the resting cardiac output.

The details of the procedure and method of determinations of the test substances have been published before.[21]

After the resting determination, some patients performed a graded amount of exercise, recumbent, on a bicycle ergometer.[8,9] The clearance values, cardiac output, and blood pressures were again determined during at least 10 to 15 minutes of exercise.

In some patients determinations were repeated several times during the intravenous infusion of isotonic glucose solution at a rate of about 25 ml./min.[7]

Some patients in the present series were studied again after the heart lesion had been totally or partly corrected by surgical treatment. The patients were operated on in the Surgical Department, Sabbatsberg Hospital.

RESULTS

Table I contains the figures for cardiac output, stroke volume, blood pressures, and renal clearances obtained during rest. The lowest renal blood flow and glomerular filtration rate were found in constrictive pericarditis, mitral valvular disease of functional Group 4, aortic valvular disease of Groups 3 and 4,

TABLE I. CARDIAC OUTPUT AND BLOOD PRESSURES IN THE PULMONARY AND SYSTEMIC CIRCULATION AND RENAL CLEARANCES FOR INULIN AND PARA-AMINOHIPPURATE IN 146 CASES OF VARIOUS HEART OR LUNG DISORDERS

DIAGNOSIS	NO. CASES	CARDIAC OUTPUT L./MIN.	STROKE VOLUME ML./BEAT	BLOOD PRESSURES MM. HG				ART. O_2 SATUR. (%)	CLEARANCES ML./MIN.	
				RA	PCV	PA	BA		PAH	INULIN
Auricular defect										
A.	3	16.4*	194	3	6	28	85	93	482	139
B.	7	12.6*	159	1	4	12	75	95	502	126
Patent ductus arteriosus										
A.	4	6.5	76	1	10	31	87	93	431	114
B.	8	6.6	75	1	7	15	89	93	473	123
Eisenmenger's complex	4	7.7	93	0	7	89	89	82	315	108
Coarctation of the aorta	5	6.5	81	0	6	16	93	94	468	135
Dilatation of pulmonary arch	3	7.2	86	2	5	10	89	94	609	132
Primary pulmonary hypertension	2	5.0	57	3	4	54	84	87	335	103
Pulmonary diseases	5	5.2	65	−3	8	26	79	86	367	112
Constrictive pericarditis	4	6.1	58	13	13	29	81	95	227	96
Polycytemia	2	5.8	73	−1	10	17	136	93	399	117
Hypertensive cardiovascular disease	15	6.8	85	0	6	13	150	95	302	91
Aortic valvular disease										
Groups 1, 2	9	7.7	87	1	8	14	89	95	480	138
Groups 3, 4	3	6.2	72	2	14	34	97	95	295	78
Mitral valvular disease										
Groups 1, 2	26	6.2	78	1	13	20	91	93	405	109
Group 3	32	4.7	57	2	21	38	94	92	323	100
Group 4	7	3.6	37	2	24	53	98	83	216	76
Groups 3-4 RHF	7	3.3	44	9	26	68	96	90	205	83

A, mean pulmonary arterial pressure above 20 mm. Hg; *B*, mean pulmonary arterial pressure below 20 mm. Hg; Groups 1-4 classified according to New York Heart Association.

RHF = right heart failure; PAH = para-aminohippurate; RA = right auricle; PCV = pulmonary capillary venous; PA = pulmonary artery; BA = brachial artery.

*Pulmonary blood flow.

and arterial hypertension. The patients with Eisenmenger's complex, primary pulmonary hypertension and pulmonary disease, and those with mitral valvular disease of Group 3 had also considerably decreased renal blood flow.

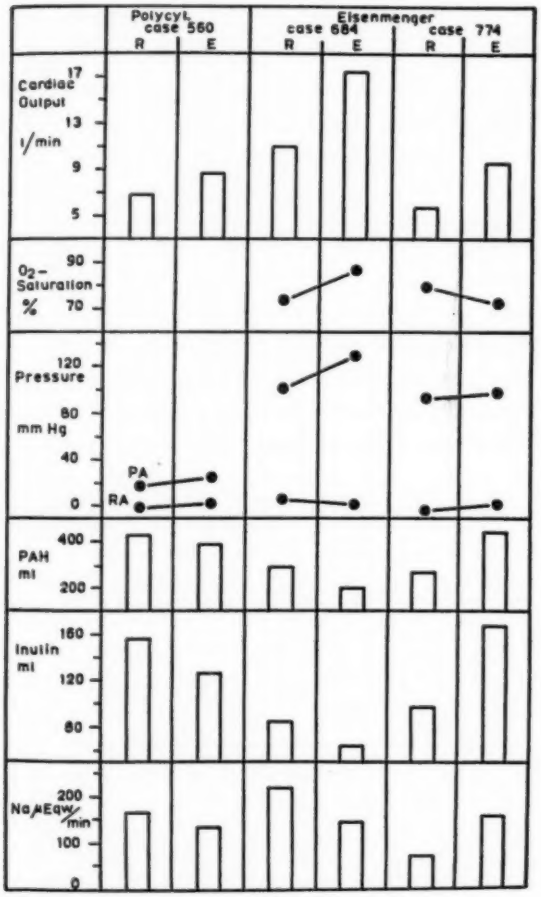


Fig. 1.—Cardiac output (systemic flow), blood pressures, renal clearances and renal excretion of sodium in one patient with polycythemia and in two patients with Eisenmenger's complex studied during rest and exercise.

R **= resting values;** ***E*** **= values obtained during exercise.**

Na = sodium excretion in μ Eq./min. Legends as in Table I.

Those patients with dilatation of the pulmonary arch only had completely normal values for renal perfusion, while all other listed patients had slightly decreased blood flow with a normal filtration rate.

In all patients except seven with mitral valvular disease in right-heart failure and the four with constrictive pericarditis, the right auricular pressure was normal. The patients with elevated auricular pressure had the lowest renal blood flow of all studied, but there were also other groups with normal right auricular pressure and an equally low renal blood flow.

There was no correlation between arterial oxygen saturation, systemic or arterial pressure in the pulmonary artery,and renal blood flow. Both in patients

with auricular septal defect and patent ductus arteriosus was the renal plasma flow equal in the groups with elevated and in the groups with normal pulmonary arterial pressure.

There was no general correlation between the cardiac output and the renal plasma flow. There was some correlation between the stroke volume and the renal function; the patient with the lowest renal plasma flow also had the smallest stroke volume.

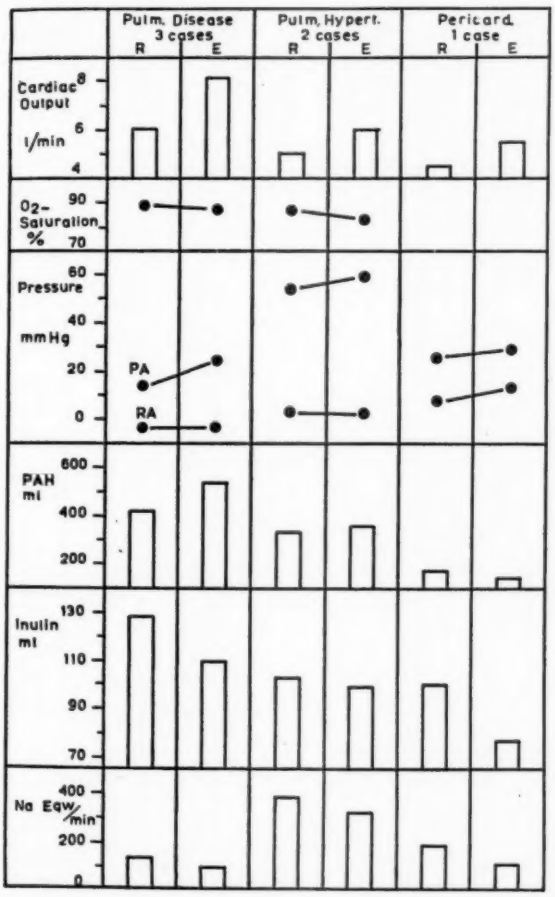


Fig. 2.—Cardiac output, blood pressures, renal clearances, and renal excretion of sodium in three patients with lung disease, two patients with primary pulmonary hypertension, and one with constrictive pericarditis studied during rest (*R*) and exercise (*E*).

The effect of graded exercise is graphically represented in Figs. 1 to 4.

Of two patients with Eisenmenger's complex one showed a decrease of renal plasma flow, filtration rate and sodium excretion during exercise, concomitant with an increase in oxygen saturation, while the opposite was found in the other patient. In both, the systemic blood flow increased adequately and the pulmonary arterial pressure increased somewhat. The auricular pressure was unaltered (Fig. 1).

Similar alterations were found in patients with lung disease (Fig. 2).

In a patient with polycythemia the renal clearances and sodium excretion decreased slightly with only slight increase in pressures in the pulmonary circulation (Fig. 1).

In constrictive pericarditis the low cardiac output increased as did the pressures in the pulmonary artery and right auricle. The renal plasma flow decreased only slightly; the inulin clearance and sodium excretion showed a more marked fall.

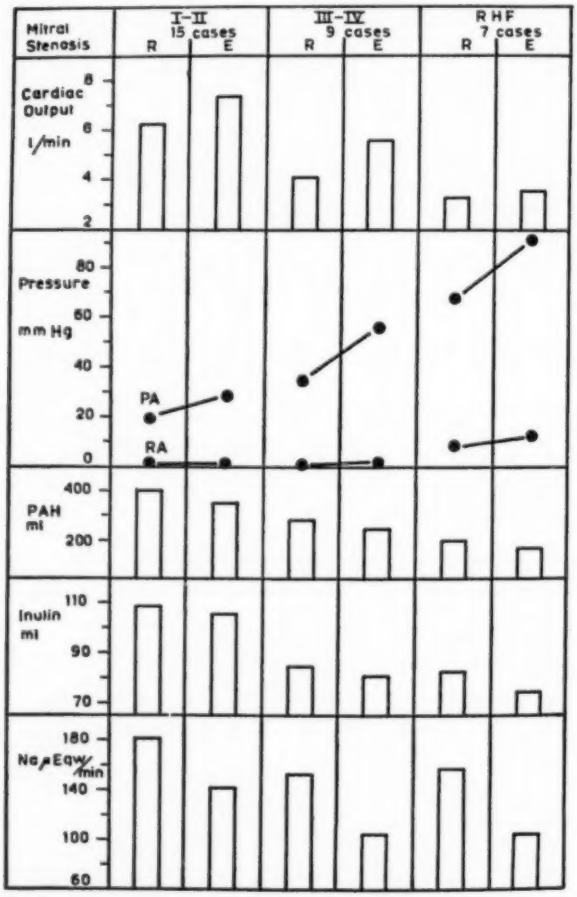


Fig. 3.—Cardiac output, blood pressures, renal clearances and sodium excretion in 31 patients with mitral stenosis, studied during rest (*R*) and exercise (*E*). There is no principal difference in the behavior of the renal function between the cases with normal and those with elevated auricular pressure.

In mitral valvular disease, exercise caused a significant drop in renal plasma flow in all patients except in those in right-heart failure where there was only a slight decrease in the renal plasma flow. Only in this last group did the auricular pressure increase but the cardiac output did not change. In the other patients the total blood flow increased without any alteration in right auricular pressure. In all patients the sodium excretion decreased in about the same amount, and the pulmonary arterial pressure always increased, more markedly in the more incapacitated patients (Fig. 3).

In hypertensive cardiovascular disease those patients who had elevated pressure in the pulmonary artery, had decreased renal plasma flow and sodium excretion during exercise, while in those with normal pulmonary blood flow, the renal plasma flow was unaltered (Fig. 4).

The findings in one patient with patent ductus arteriosus before and after surgical correction are represented in Fig. 5. The pressures in the pulmonary and systemic circuits were normal before and after surgery. The renal plasma flow increased to normal values after operation (the patient was studied about six weeks after the operation).

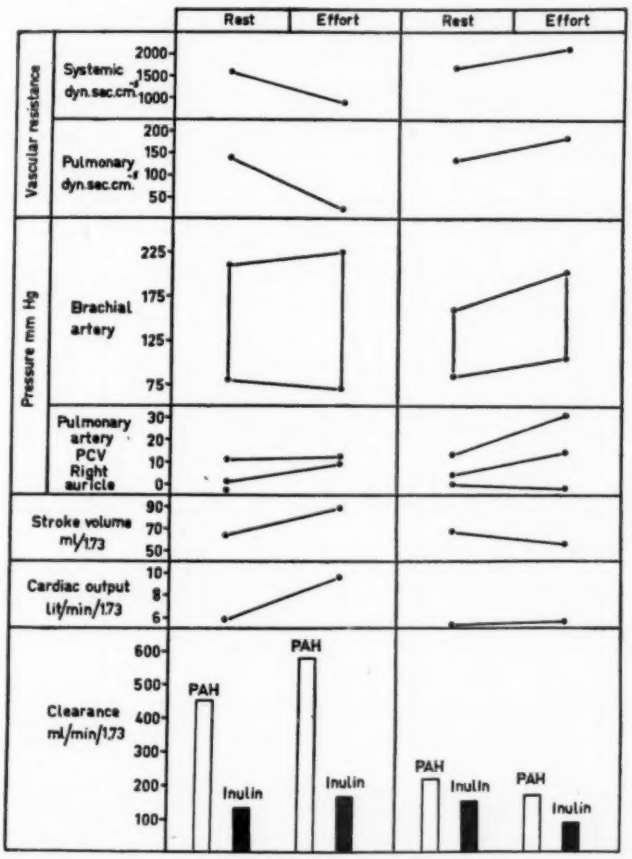


Fig. 4.—Cardiac output, blood pressures, renal clearances, pulmonary and systemic vascular resistance in two patients with hypertensive cardiovascular disease studied during rest and exercise. Note the decrease in stroke volume and renal clearances in the second case with increased pressures in pulmonary circuit and increased vascular resistance. The first case reacted with increase in stroke volume and renal plasma flow.

Similar findings in one patient with auricular septal defect and pulmonary stenosis are given in Fig. 6. In between the measurements the auricular septal defect had been closed. After operation the pulmonary blood flow had diminished to normal values, and the pressure drop from right ventricle to the pulmonary artery had decreased. The renal plasma flow increased but not to a normal level. The patient still had an abnormal response to exercise after the

operation with increase in systolic blood pressure in the right ventricle. The right auricular pressure was normal at rest and during exercise.

The renal plasma flow was also measured before and after commissurotomy in 25 patients with mitral stenosis. In several the blood flow changed toward normal, but there was poor correlation between the improvement of the pulmonary and the renal circulation. An example of this in Fig. 7 shows a patient with mitral stenosis studied during the rapid infusion of isotonic glucose before and after surgery. At rest the total blood flow increased and the pressures in the pulmonary artery decreased, but the renal clearances were rather lowered after operation.

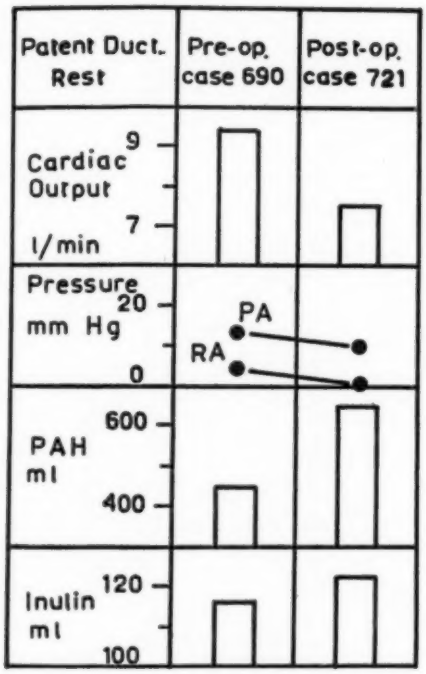


Fig. 5.

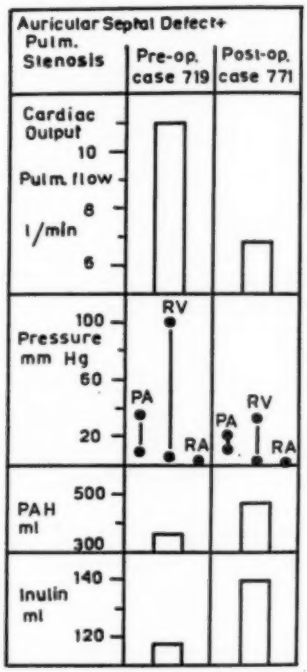


Fig. 6.

Fig. 5.—Cardiac output, blood pressures and renal clearances in one patient with patent ductus arteriosus before and after surgical treatment.

Fig. 6.—Pulmonary blood flow, blood pressures and renal clearances in one patient with combined auricular spetal defect and pulmonary stenosis before and after surgical treatment of the heart defects.

The renal reaction to the glucose infusion was equal in both instances, immediate increase in renal plasma flow and filtration to normal values with a gradual and marked increase in sodium excretion. The cardiac output increased to a normal level in the study before operation and stayed normal afterwards. The pressure in the pulmonary artery increased somewhat during the infusion preoperatively, but in the study following operation it first increased and then fell to normal values.

The results of the same procedure in a patient with pulmonary fibrosis appear in Fig. 8. The renal clearances increased immediately to high normal

values but returned to slightly depressed levels. The sodium excretion increased about twentyfold during the rapid infusion. The cardiac output increased, but the pressures in the pulmonary circuit were unaltered.

DISCUSSION

The renal blood flow is markedly reduced in congestive heart failure, usually with a concomitant reduction of the glomerular filtration rate.[1,6,10,11,14-16] In most cases reported in the literature, the renal blood flow increases only slightly when compensation is restored and does not reach normal figures.[6] It

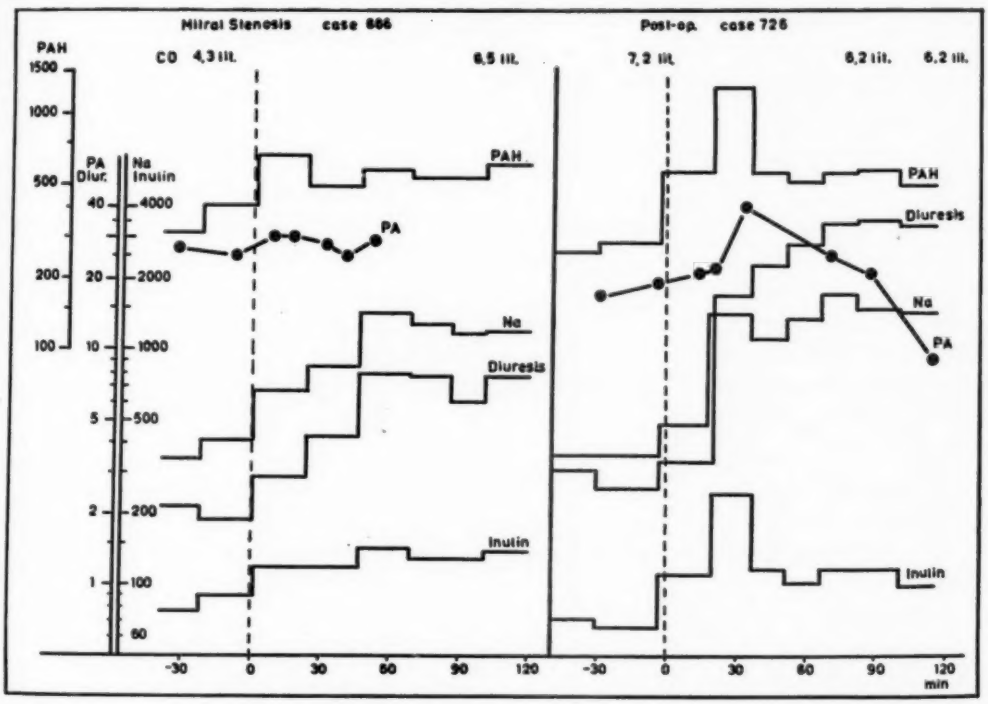


Fig. 7.—Renal clearances and excretion of sodium and water, cardiac output and pulmonary arterial blood pressure in one patient with mitral stenosis before (Case 666) and after (Case 726) valvulotomy. Resting values to the left of the dotted line. Values during a rapid continuous infusion of an isotonic glucose solution to the right. Note that the clearances and sodium excretion reach the same high values during the infusion both before and after the operation irrespective of resting values.

has been questioned whether the remaining impaired function manifested as depressed renal blood flow is due to emotional factors initiated by the study, clinically unrecognizable renal disease, arteriosclerotic or degenerative changes of the kidneys, or to the previous heart failure. Results of renal studies in patients with mitral valvular disease who never had been in heart failure indicate that the decreased renal plasma flow found in these patients could not be due to any of these factors but must in some way be connected with the heart disorder per se.[20,21]

Three of the most important modifications of the circulation that may occur in heart disease are elevated blood pressures in the pulmonary circuit, depressed systemic blood flow, and finally elevated right auricular (and venous) pressure. In patients with mitral valvular disease the decrease of renal blood flow is roughly correlated to the degree of pulmonary hypertension and the

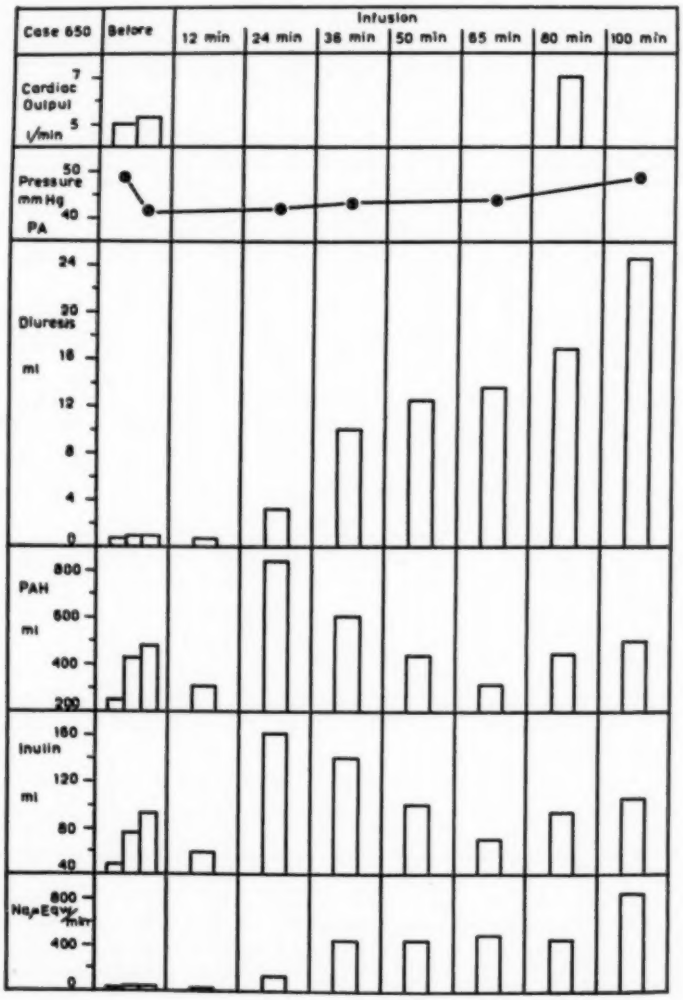


Fig. 8.—Renal clearances, excretion of sodium and water, cardiac output and pulmonary arterial blood pressure in a patient with pulmonary fibrosis. Values obtained at rest and at various time intervals during a rapid continuous infusion of an isotonic glucose solution.

depression of the cardiac output.[20,21] Elevated renal venous pressure, on the contrary, does not seem to contribute much to this effect.[21] Of any single item the reduction in renal blood flow is best correlated to the increase in pulmonary arterial pressure.[20]

Of other heart disorders investigated in the present study, the lowest renal clearances were found in patients with constrictive pericarditis and aortic

valvular disease in manifest or impending left ventricular failure. The patients with constrictive pericarditis had slightly elevated pressures in the pulmonary circulation, increased right auricular pressure, and a low cardiac output (3 out of 4) with a low-stroke volume. The patients with aortic disease had moderately elevated pressures in the pulmonary circulation, normal right auricular pressure, and fairly normal cardiac output and stroke volume. Other disorders exhibiting rather marked impairment of renal function were primary pulmonary hypertension and Eisenmenger's complex. The patients in these groups had lowered arterial oxygen saturation, increased pulmonary arterial pressure with normal pulmonary capillary venous and right atrial pressures, and normal or low systemic blood flow.

Thus in all cases, where the reduction of renal blood flow was marked (para-aminohippurate clearance below 350 ml./min.) the pressure in the pulmonary artery was moderately or markedly elevated. In no patient, however, was this increased pressure the only hemodynamic abnormality present, but always accompanied by either decreased cardiac output, arterial unsaturation, or increased right-atrial pressure.

The possible relationship of elevated pulmonary arterial pressure to the renal function was studied in the patients with auricular septal defect or patent ductus arteriosus. When the material was divided after the presence of elevated pulmonary arterial pressure no difference regarding renal function between the two groups was found. The pressure increase was, however, moderate in most cases. This finding indicates that at least moderately increased pressures in the pulmonary circuit do not necessarily influence the renal blood flow. The apparent correlation in the other patient groups may be due to the fact that increased pressure in the pulmonary circuit is an indication of the severity of the heart lesion and may parallel any other function expressing the same item.

Results of the acute experiments point in the same direction. During exercise the same correlation between the pulmonary artery pressure and the renal blood flow seemed to exist in the patients with mitral valvular disease.

In other patients, however, like those with pulmonary heart disease, primary pulmonary hypertension, or Eisenmenger's complex the blood flow through the kidneys increased simultaneously with an increase in the pulmonary arterial blood pressure. The concomitant decrease in arterial oxygen saturation probably exerted some modifying effect. During rapid intravenous infusion of an isotonic glucose solution in the patients with mitral valvular disease the pressure likewise increased concomitant with an increase in renal blood flow.[7] The same phenomenon has also been found when a mixture of noradrenaline and Apresoline[22] was given to patients with mitral valvular disease.

As for the cardiac output the present material does not allow for any definite trends regarding the relationship to the renal blood flow. Depression of the cardiac output was usually associated with a marked degree of pulmonary hypertension. It is understandable that the renal blood flow is decreased when the cardiac output is low.

On the other hand, the reduction in renal plasma flow observed in the patients with normal cardiac output is not easily accounted for. In some of

these patients the stroke volume was low although the minute output was normal. Thus decreased renal blood flow was better correlated to low-stroke output.

Brod and his associates,[3] studying the renal blood flow and renal fraction of the cardiac output, reached the conclusion that adrenergic impulses were responsible for the decreased renal blood flow in patients with congestive heart failure. The results of the present study suggest that such a mechanism may contribute to the diminished renal blood flow in severe heart disease before any signs of congestion are apparent. In many instances a probable factor causing the release of adrenergic impulses would then be decreased stroke volume. In other patients it was impossible to demonstrate any single hemodynamic factor responsible for such a release. The findings in the present material vary thus within wide limits, emphasizing the complexity of the factors involved.

The right auricular pressure in the present material was elevated in few patients only. It has been shown experimentally that increased renal venous pressure may depress the renal blood flow and filtration rate in a similar fashion to what is found in heart disease.[2] Most of the patients with low renal perfusion had, however, a normal auricular pressure. Only in those with constrictive pericarditis may the high renal venous pressure have contributed to the renal findings.

The only conclusion that can be reached from the present study regarding the renal blood flow in heart disease is that it is decreased in most forms of cardiovascular disorders, roughly in proportion to the severity of the heart lesion. In patients with minor disorders, which seldom have serious consequences and usually never progress to congestive heart failure, like auricular septal defects or patent ductus arteriosus with small shunts, the renal blood flow is only slightly decreased. The same is also true in patients with mitral or aortic valvular disease with essentially normal hemodynamic findings. In patients with severe heart disease with increased pressures in the pulmonary circulation and decreased cardiac output, the renal blood flow is greatly reduced regardless of whether the patient has signs of right-heart failure or not. Most of these patients actually are on the border to such failure and will eventually develop failure if they are not vigorously treated and mostly kept in bed.

The results obtained in the patients with hypertensive cardiovascular disease were included in the present report only to demonstrate the similarity between the renal dynamics in that disorder and in severe heart disease. It seems, however, clear that the alterations in renal circulation in hypertensive cardiovascular disease are not strictly comparable to what is found in other diseases of the cardiovascular system. The only hemodynamic disturbance found in these patients was the increased arterial blood pressure, while the total blood flow, pressures in the pulmonary circuit, and right auricular pressure were normal.

It can be questioned whether the marked alterations of the renal dynamics found in severe heart disease are due to anatomic lesions in the kidneys or if they are of a reversible nature. The effects of surgical correction of the minor heart lesions were found to cause a reversal to normal of the renal function.

In patients with mitral valvular disease, however, commissurotomy was found to give only minor changes in renal function, mostly toward normal values.[23] The results of the studies with a rapid infusion of isotonic glucose solution clearly demonstrated the ability of the kidneys in the same patients to augment the perfusion up to normal values or even higher.[7] This increase in renal blood flow took place simultaneously with an increase in cardiac output and pressures in the pulmonary artery.

The sodium excretion was studied during the exercise tests and the rapid infusion of isotonic glucose solution. The sodium excretion usually fell when the blood flow decreased and rose when the renal blood flow increased. There was, however, no close correlation between changes in sodium excretion and renal blood flow. The correlation to the glomerular filtration rate was also poor. It was not possible to find any single or a combination of hemodynamic features that correlated with changes in sodium output. The material does not allow the comparison of the basal values for sodium output or clearance in the various heart disorders.

The normal individual responded to the glucose infusion with marked diuresis but without any increase in sodium excretion. In the patients with mitral valvular disease, pulmonary fibrosis or arterial hypertension, the infusion of glucose solution caused a marked increase in sodium excretion. The mechanism for this finding is beyond the scope of this paper.

Not only in the cases of mitral valvular disease with marked hemodynamic alterations but also in those with mitral valvular disease and essentially normal circulation at rest, an abnormal renal reaction to both exercise and glucose infusion was demonstrated. The normal individual did not alter either renal blood flow or sodium excretion, but all patients with mitral disease decreased these functions during exercise and increased them during infusion regardless of the severity of the valvular lesion. These results clearly indicate that early in the course of these diseases altered renal function is important. The sodium excretion is in some way or other disturbed long before any signs of right-heart failure appear. There was no close relationship between the changes in sodium excretion and changes in renal blood flow during these acute experiments. It is, however, possible that the decrease in renal blood flow found in almost all cases with cardiovascular disease is an expression for the same influence that causes the altered sodium handling by the kidneys in patients with heart diseases.

SUMMARY AND CONCLUSIONS

1. The cardiac output and blood pressures in the pulmonary and systemic circulation were determined simultaneously with the renal clearances for inulin and para-aminohippurate in 146 cases of various heart diseases.

2. The same values were determined both at rest and during exercise in the majority of the cases.

3. In some cases the study was repeated after surgical correction of the heart lesion.

4. In some cases of mitral valvular disease, pulmonary fibrosis, and arterial hypertension, the reaction to a rapid infusion of isotonic glucose was also studied.

5. The renal blood flow was lower than normal in all cases with cardiovascular disease, roughly proportional to the severity of the heart disease. The decreased renal blood flow was usually found together with decreased stroke volume, but elevated renal venous pressure seemed to contribute to the decreased blood flow not at all or only a little. Studies during exercise also pointed to the minor importance of the elevated venous pressure for the renal changes.

6. The renal blood flow increased to normal, when a case with patent ductus was surgically corrected and towards normal in a case with auricular septal defect and pulmonary stenosis, when the defect was closed. When cases with mitral stenosis were operated on, the renal blood flow showed variable changes, although a slight increase usually was found when the pulmonary circulation was improved.

7. When isotonic glucose was infused at a rate of 25 ml./min., the renal blood flow increased to normal in cases with mitral stenosis or pulmonary fibrosis. The sodium excretion increased successively to several times the basal value. This reaction is the same as in cases with arterial hypertension and is not found in normal individuals.

8. These findings indicate that cases with heart disease prone to develop congestive failure, long before any signs of failure have appeared, exhibit changes in renal circulation and sodium handling.

SUMMARIO IN INTERLINGUA

Simultanee studios hemodynamic e renal esseva executate in 146 patientes con varie morbos cardiac. Le fluxo de sanguine renal esseva subnormal in omne casos, plus o minus proportionalmente al severitate del lesion cardiac. Le volumine per pulso esseva infra le norma. Studios a exercitio indicava que iste basse fluxo de sanguine renal non resultava ab un elevate pression venose. Il se monstrava que chirurgia cardiac produceva normalisation del fluxo sanguinee renal in patientes con ducto patente o defecto auriculoseptal e un minor augmento de ille fluxo in patientes con stenosis mitral si e quando le circulation pulmonar se habeva meliorate. In patientes con stenosis mitral o con fibrosis pulmonar, un solution isotonic de glucosa (infundite a un ration de 25 ml per minuta) normalisava le fluxo sanguinee renal e augmentava le excretion de natrium a plure vices le valores basal. Iste reaction se trovava etiam in patientes hypertensive sed non in subjectos normal.

Nos conclude que in patientes de morbo cardiac qui es pron a disveloppar dysfunctionamento congestive, alterationes in le circulation renal e etiam in le economia de natrium precede per longe le prime signos clinic del dysfunctionamento.

The cooperation of Dr. Clarence Crafoord and his colleagues of Sabbatsberg Hospital, Stockholm, Sweden, is acknowledged.

REFERENCES

1. Aas, K., and Blegen, E.: The Renal Blood Flow and the Glomerular Filtration Rate in Congestive Heart Failure and Some Other Clinical Conditions, Scandinav. J. Clin. & Lab. Invest. **1**:22, 1949.
2. Blake, W. D., Wégria, R., Keating, R. P., and Ward, H. P.: Effect of Increased Renal Venous Pressure on Renal Function, Am. J. Physiol. **175**:1, 1949.
3. Brod, J., Fejfar, Z., and Fejfarová, M. H.: The Rôle of Neurohumoral Factors in the Genesis of Renal Hemodynamic Changes in Heart Failure, Acta med. scandinav. **148**:273, 1954.
4. Bucht, H.: Studies on Renal Function in Man, Scandinav. J. Clin. & Lab. Invest., supp. 3, **3**:1, 1951.
5. Cournand, A., and Ranges, H. A.: Catheterization of the Right Auricle in Man, Proc. Soc. Exper. Biol. & Med. **46**:462, 1941.
6. Eichna, L. W., Farber, S. J., Berger, A. R., Earle, D. P., Rader, B., Pellegrino, E., Albert, R. E., Alexander, D. J., Taube, H., and Youngwirth, S.: Cardiovascular Dynamics, Blood Volumes, Renal Functions and Electrolyte Excretions in the Same Patients During Congestive Heart Failure and After Recovery of Cardiac Compensation, Circulation **7**:674, 1953.
7. Ek, J., Varnauskas, E., Thomasson, B., Bucht, H., and Werkö, L.: Studies on the Renal Circulation and Renal Function in Mitral Valvular Disease. IV. Effect of Rapid Intravenous Infusion of Isotonic Glucose Solution (To be published).
8. Eliasch, H.: The Pulmonary Circulation at Rest and on Effort in Mitral Stenosis, Scandinav. J. Clin. & Lab. Invest., supp. 4, **4**:,1 1952.
9. Eliasch, H., Wade, G., and Werkö, L.: The Effects of Work on the Pulmonary Circulation in Mitral Stenosis, Circulation **5**:271, 1952.
10. Grossman, J., Weston, R. E., Halperin, J. P., and Leiter, L.: The Nature of the Renal Circulatory Changes in Chronic Congestive Failure as Reflected by Renal Tubular Maximal Function, J. Clin. Invest. **29**:1320, 1950.
11. Heller, B. I., and Jacobson, E. W.: Renal Hemodynamics in Heart Disease, Am. Heart J. **39**:188, 1950.
12. Lagerlöf, H., and Werkö, L.: Studies on the Circulation in Man. I. Technique of Venous Catheterization With Determination of Cardiac Output and Simultaneous Recordings of the Blood Pressures, the Electrocardiogram, Phonocardiogram and Respiration, Acta med. scandinav. **132**:495, 1947.
13. Lagerlöf, H., and Werkö, L.: Studies on the Circulation in Man. VI. The Pulmonary Capillary Venous Pressure Pulse, Scandinav. J. Clin. & Lab. Invest. **1**:147, 1949.
14. Maxwell, M. H., Breed, E. S., and Schwartz, I. L.: Renal Venous Pressure in Chronic Congestive Heart Failure, J. Clin. Invest. **29**:342, 1950.
15. Merrill, A. J.: Edema and Decreased Renal Blood Flow in Patients With Chronic Congestive Heart Failure: Evidence of "Forward Failure" as the Primary Cause of Edema, J. Clin. Invest. **25**:389, 1946.
16. Merrill, A. J., and Cargill, W. H.: The Effect of Exercise on the Renal Plasma Flow and Filtration Rate of Normal and Cardiac Subjects, J. Clin. Invest. **27**:272, 1948.
17. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Blood Vessels, ed. 5, New York, 1953, The Criteria Committee of the New York Heart Association, Inc.
18. Sinclair-Smith, B., Kattus, A. A., Genest, J., and Newman, E. V.: Changes in the Renal Mechanisms of Electrolyte Excretion and the Metabolic Balances of Electrolytes and Nitrogen in Congestive Cardiac Failure With Exercise, Rest and Aminophyllin, Bull. Johns Hopkins Hosp. **84**:369, 1949.
19. Tybjaerg-Hansen, A.: Pressure Measurement in the Human Organism, Copenhagen, 1949, Teknisk Forlag.
20. Werkö, L., Ek, J., Bucht, H., and Eliasch, H.: Correlation Between Renal Hemodynamics, Cardiac Output and Right Heart Pressures in Mitral Valvular Disease, Scandinav. J. Clin. & Lab. Invest. **4**:15, 1952.
21. Werkö, L., Varnauskas, E., Eliasch, H., Ek, J., Bucht, H., Thomasson, B., and Bergström, J.: Studies on the Renal Circulation and Renal Function in Mitral Valvular Disease. I. Effect of Exercise, Circulation **9**:687, 1954.
22. Werkö, L., Varnauskas, E., Ek, J., Bucht, H., Thomasson, B., Bergström, J., and Eliasch, H.: Studies on the Renal Circulation and Renal Function in Mitral Valvular Disease. II. Effect of Apresoline, Circulation **9**:700, 1954.
23. Unpublished observations.

PULMONARY STENOSIS WITH INCREASED PULMONARY BLOOD FLOW

FREDERIC L. ELDRIDGE, M.D.,* AND HERBERT N. HULTGREN, M.D.**

SAN FRANCISCO, CALIF.

SEVERAL recent papers have described cases of pulmonic stenosis associated with defects of the cardiac septa in which prominent left-to-right intracardiac shunts with increased pulmonary blood flow have been present, instead of the more commonly expected right-to-left shunt.[1-4] It is apparent that such cases are not rare and because of this fact they present several interesting questions:

1. What is the actual incidence of such lesions as compared to other varieties of congenital heart disease?

2. What are the essential clinical features of these cases that would permit accurate diagnosis?

3. Since in the more familiar instance of a defect of the cardiac septum associated with a pulmonic stenosis there is a right-to-left shunt, what are the physiologic features of these cases in which a pure arteriovenous shunt is present?

4. Since the closure of septal defects and the incision of stenosed pulmonary valves are rapidly becoming widely available surgical procedures, what are the physiologic considerations involved in selecting the proper type of surgery in these cases?

This report has been prepared in an effort to answer these questions.

An estimate of the relative incidence of pulmonic stenosis with arteriovenous shunts may be obtained from the reports of Gøtzsche,[5] who found three cases in 201 patients studied by cardiac catheterization, and Deuchar and Zak,[2] who found four cases in 130 of their patients. Broadbent and associates[3] described ten cases; Moffitt and associates,[4] six cases; Wood,[6] six cases; and Dexter[7] and Dow[8] mention having seen cases. In approximately 250 diagnostic catheterization studies done in this laboratory, we have encountered eight cases. This is slightly less than the incidence of Eisenmenger's syndrome, of which we have studied eleven cases. It is higher than the incidence of atrial septal defects with pulmonic stenosis and mixed or right-to-left shunts of which we have seen four cases.

From the Department of Medicine of the Stanford University School of Medicine, San Francisco, Calif.

This study was aided by grants from the San Francisco Heart Association and The Fuller Foundation.

Received for publication July 6, 1954.

*Evelyn Neizer Fellow in Medicine.

**Scholar in Medical Science of the John and Mary R. Markle Foundation.

The cases in this report were selected especially for the reason that none showed any suggestion of a significant venoarterial shunt, and in none was there any evidence of cyanosis at any time. Coexisting with the pulmonary stenosis, four had interventricular septal defects, three had interatrial septal defects, and one had an aortic-pulmonary artery communication.

INTERVENTRICULAR SEPTAL DEFECTS

CASE 1.—D. A. This 16-year-old schoolboy entered Stanford University Hospital on Sept. 23, 1953. A cardiac murmur had been detected soon after birth, but growth and development had proceeded normally and the only incapacity had been slight dyspnea and palpitation on exertion.

Physical examination revealed a tall thin boy who looked well. Blood pressure in the arm was 110/64 mm. Hg. A precordial chest bulge was present to the left of the sternum, and a prominent systolic heave was felt in the same region. A loud harsh systolic murmur, heard best in the left first and second intercostal spaces, was transmitted widely over the precordium. A systolic thrill was present in the same area. The second sound in the pulmonary area was split with a moderately loud second component. There was no evidence of cyanosis.

The hemoglobin was 15.0 grams/100 c.c., and the hematocrit was 44 per cent.

The electrocardiogram (Fig. 1*A*) was compatible with right ventricular hypertrophy.

Fluoroscopy and x-rays of the chest and heart (Fig. 2) revealed marked right ventricular enlargement, pulmonary plethora with a prominent pulmonary artery segment, and large peripheral pulmonary vessels. A "hilar dance" was noted at fluoroscopy.

The results of cardiac catheterization performed on Sept. 29, 1953, are shown in Table I.

TABLE I. FINDINGS ON CATHETERIZATION* IN CASE 1

LOCATION	O_2 CONTENT C.C./100 C.C.	O_2 SATURATION (%)	PRESSURE, MM. HG S/D/MEAN
Superior vena cava	13.9	71	
Right atrium	13.4	68	-/-/5
Right ventricle	16.5	84	90/9
Pulmonary artery	16.9	86	30/13/24
Pulmonary artery	17.0	86	
Femoral artery	17.9	91	110/67
O_2 capacity	19.7		

O_2 Consumption†	230 c.c./min.
Systemic flow	5.1 L./min.
Pulmonary flow‡	12.7 L./min.
L-R shunt	8.4 L./min.
R-L shunt‡	0.8 L./min.

*Oxygen determinations performed on the Van Slyke apparatus. Pressures recorded by means of Hamilton manometers.

†Estimated

‡Based upon an assumed 95 per cent oxygen saturation of pulmonary vein blood.

Comment.—On the basis of the x-ray finding of pulmonary plethora, this patient was thought to have an atrial septal defect and perhaps an interventricular septal defect to explain the location of the murmur. The moderately loud pulmonic second sound was thought to be incompatible with a pulmonic

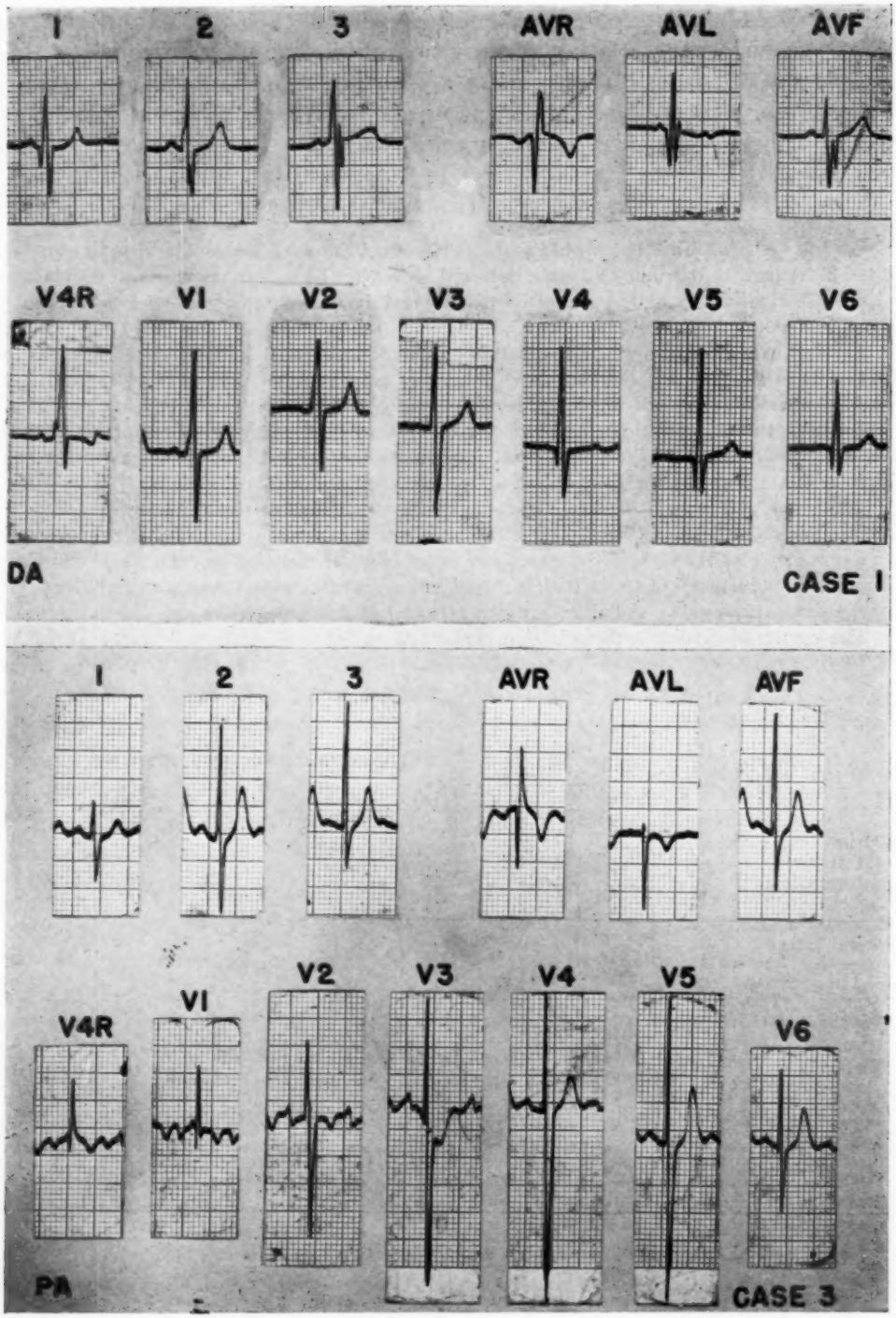


Fig. 1*A*.—*(For legend see opposite page.)*

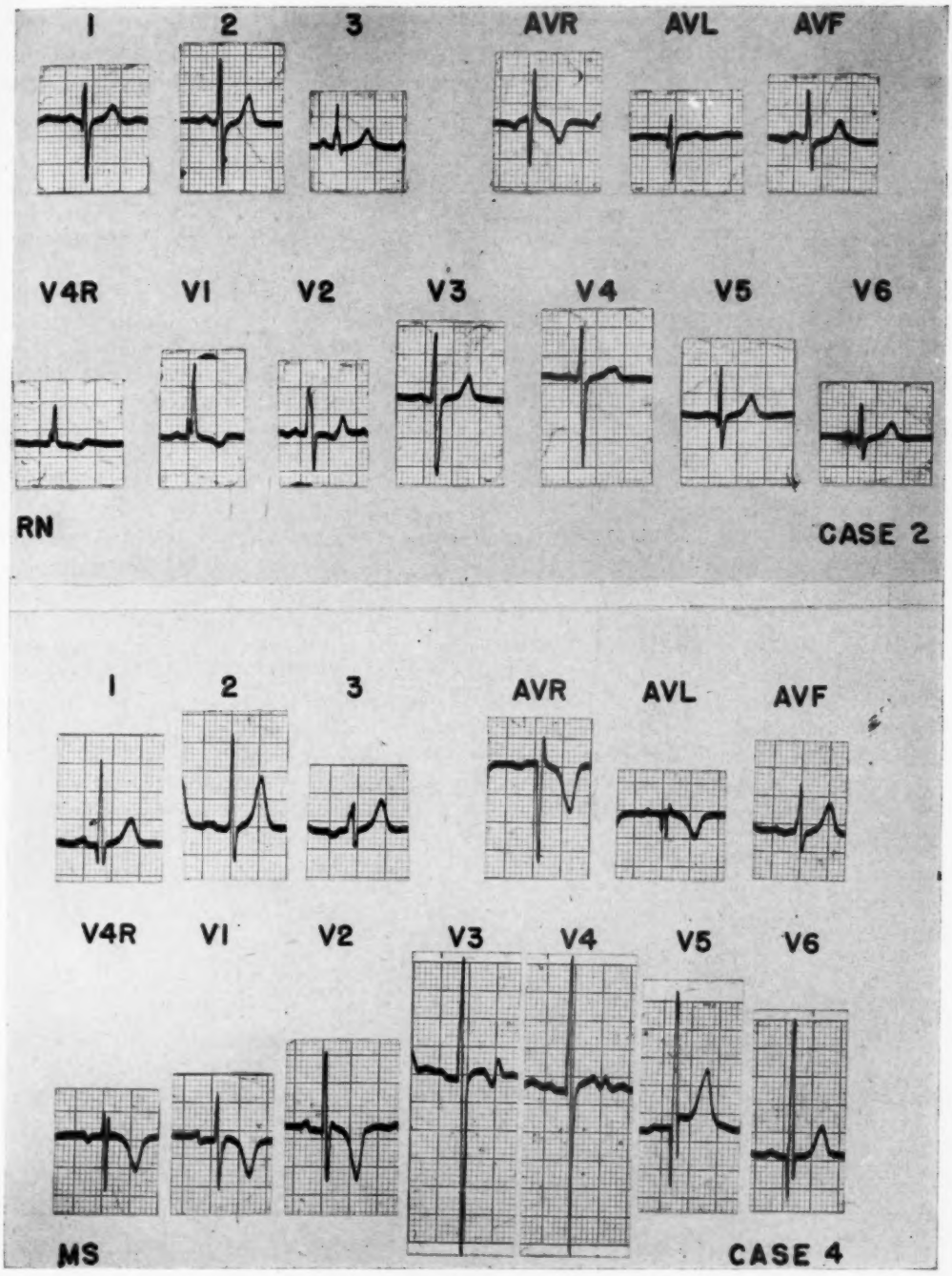


Fig. 1*B*.

Fig. 1.—*A* and *B*. Electrocardiograms in four cases of pulmonic stenosis with interventricular septal defect.

stenosis. Cardiac catheterization clearly demonstrated the presence of a pulmonic stenosis of moderate degree (pressure tracing, Fig. 3) and a ventricular septal defect with an increased pulmonary blood flow. The pulmonary artery pressure was slightly elevated.

CASE 2.—R. N. This 6-year-old boy entered Stanford University Hospital on June 22, 1953. At about 1 year of age a cardiac murmur had been noted on routine examination. The patient had experienced, at the age of 3, one episode of bronchopneumonia from which recovery was apparently complete. The only symptom at the time of admission was slight dyspnea after exertion.

Physical examination revealed a healthy-looking well-developed boy. Blood pressure in the arm was 104/60 mm. Hg. Moderate bulging of the left anterior chest was present. A systolic thrill maximal in the third and fourth intercostal spaces to the left of the sternum was felt. There was a harsh systolic murmur along the left sternal border, heard best in the first and second intercostal spaces. The pulmonary component of the second sound was not heard. On one occasion cyanosis was said to have developed after exercise, but this could not be corroborated with the child under observation.

The erythrocytes were 5.2 million/c.mm. with 12.3 grams/100 c.c. of hemoglobin and a hematocrit of 36 per cent.

The electrocardiogram (Fig. 1*B*) showed an incomplete right bundle branch block and right ventricular hypertrophy.

Fluoroscopy and x-rays of the chest and heart (Fig. 2) revealed a normal over-all size of the heart and evidence of right ventricular enlargement. A right aortic arch was present. The pulmonary vessels were normal and there was no enlargement of the pulmonary artery segment.

Cardiac catheterization was performed on June 25, 1953. The catheter tip was passed through an interventricular septal defect and into the aorta (Fig. 2). Results of the study are shown in Table II.

TABLE II. FINDINGS ON CATHETERIZATION IN CASE 2

LOCATION	O_2 CONTENT C.C./100 C.C.	O_2 SATURATION (%)	PRESSURES, MM. HG S/D/MEAN
Superior vena cava	10.6	71	
Inferior vena cava	12.3	82	
Average venae cavae	11.5	77	
Right atrium	11.2	75	-/-/7
Low right ventricle	12.1	81	76/5
High right ventricle	12.7	85	
Pulmonary artery	12.5	84	16/8/12
Aorta*	14.8	99	86/62
Femoral artery	14.3	96	102/62
O_2 capacity	14.9		
Exercise			
Capillary blood sample Right hand		94	

O_2 Consumption†	126 c.c./min.
Systemic flow	4.1 L./min.
Pulmonary flow	7.0 L./min.
L-R shunt	2.9 L./min.
R-L shunt	0

*Catheter passed through ventricular septal defect.
†Estimated.

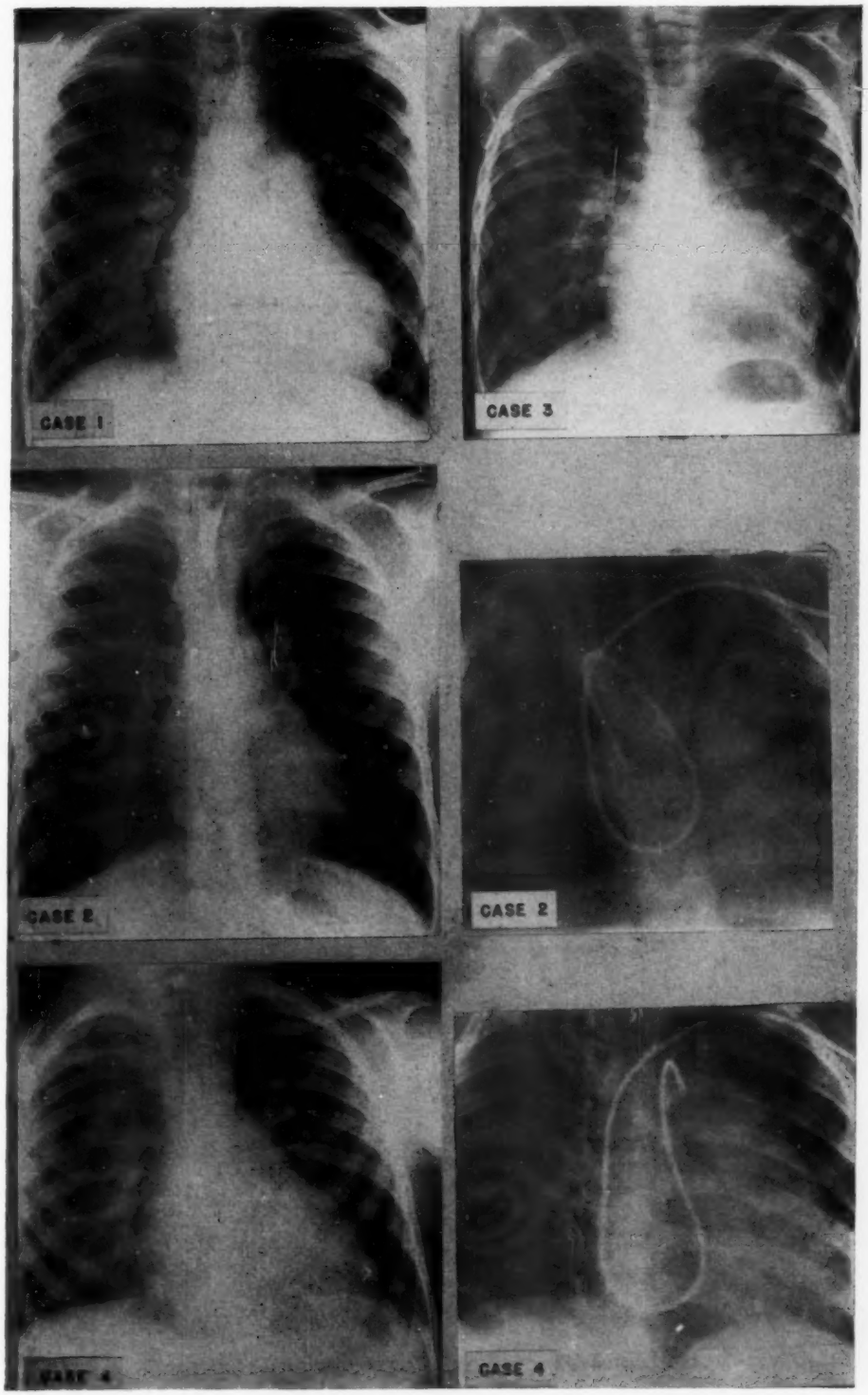


Fig. 2.—Chest x-rays in four cases of pulmonic stenosis with interventricular septal defect. Film taken at cardiac catheterization in Case 2 shows catheter passing through ventricular septal defect into right-sided aortic arch. Film taken at catheterization in Case 4 shows catheter passing through ventricular septal defect into aorta.

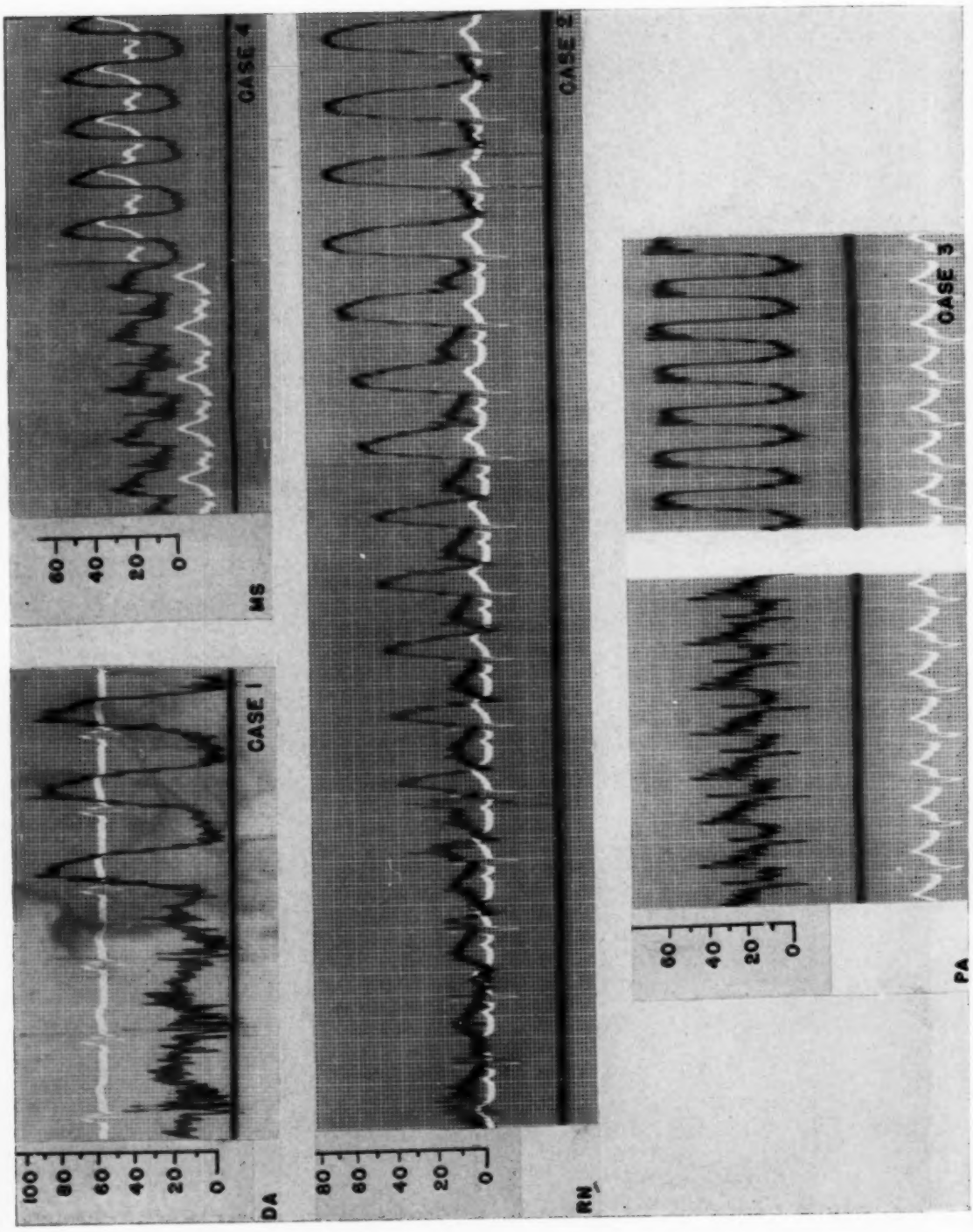


Fig. 3.—Pressure tracings from pulmonary artery (left of each tracing) and right ventricle (right of each tracing) in four cases of pulmonic stenosis with interventricular septal defect.

Comment.—The pressure tracings indicate the presence of an infundibular type of pulmonic stenosis (Fig. 3) associated with an interventricular septal defect with slightly increased pulmonary blood flow. Since a right-sided aortic arch is present, this case would resemble a tetralogy of Fallot except for the absence of peripheral unsaturation and cyanosis. It is of interest that this case was diagnosed as a pulmonic stenosis on the basis of physical and x-ray findings, and the interventricular septal defect was an unexpected finding.

CASE 3.—P. A. This 3½-year-old boy entered Stanford University Hospital on June 11, 1952. A cardiac murmur had been discovered on routine examination at the age of 5 months. The only complaints had been easy fatigability, a susceptibility to colds, and a somewhat slow motor development (sat, 8 months; walked, 21 months).

Physical examination revealed a small and thin, but healthy-appearing boy. Blood pressure in the arm was 110/70 mm. Hg. A prominent precordial heave was felt to the left of the sternum. A thrill was readily palpable to the left of the sternum maximal in the third and fourth intercostal spaces. A loud systolic murmur was heard in the same area. The pulmonary component of the second sound was present but was quite soft.

The erythrocytes were 4.5 million/c.mm., the hemoglobin was 12.5 grams/100 c.c., and the hematocrit was 38 per cent.

The electrocardiogram (Fig. 1*A*) showed right ventricular hypertrophy.

Fluoroscopy and x-rays of the chest and heart (Fig. 2) revealed definite right ventricular enlargement and a suggestion of left ventricular enlargement. There was moderate engorgement of the pulmonary vessels, but no definite hilar dance was seen at fluoroscopy. The aorta was distinctly hypoplastic.

Cardiac catheterization was performed on June 12, 1952. The results are shown in Table III.

TABLE III. FINDINGS ON CATHETERIZATION IN CASE 3

LOCATION	O_2 CONTENT C.C./100 C.C.	O_2 SATURATION (%)	PRESSURES, MM. HG S/D/MEAN
Superior vena cava	10.4	69	
Low right atrium	11.1	74	
Middle right atrium	10.9	72	
Low right ventricle	10.8	71	
High right ventricle	12.7	84	64/1
Pulmonary artery	12.7	84	33/15/22
Femoral artery	14.9	99	87/51
O_2 capacity	15.1		
Exercise			
Capillary blood sample			
Right hand		96	

O_2 Consumption*	113 c.c./min.
Systemic flow	2.9 L./min.
Pulmonary flow	5.1 L./min.
L-R shunt	2.2 L./min.
R-L shunt	0

†Estimated.

Comment.—Catheterization in this case revealed evidence of moderate pulmonary stenosis (Fig. 3) and an interventricular septal defect with increased pulmonary flow. The pulmonary pressure was slightly elevated.

CASE 4.—M. S. This 4-year-old boy had been followed in this clinic since birth. At the age of 7 days a systolic heart murmur over the precordium had been noted. He had, however, developed normally and had shown no evidence of disability.

Fig. 3.—Pressure tracings from pulmonary artery (left of each tracing) and right ventricle (right of each tracing) in four cases of pulmonic stenosis with interventricular septal defect.

Physical examination showed a well-developed, healthy-appearing boy with no evidence of cyanosis. Blood pressure in the arm was 90/50 mm. Hg, in the leg 100/60 mm. Hg. A wide area of cardiac dullness was noted, and there was a left parasternal systolic lift. A thrill was present in the second to fourth intercostal spaces along the left sternal border. A loud systolic murmur was heard all over the precordium but maximally in the third and fourth intercostal spaces along the left sternal border. A faint short early diastolic murmur was heard at the apex. The pulmonic component of the second sound was loud.

The erythrocytes were 4.7 million/c.mm., the hemoglobin was 10.0 grams/100 c.c., and the hematocrit was 40 per cent.

The electrocardiogram (Fig. 1*B*) revealed somewhat bizarre biphasic QRS complexes in the precordial leads.

Fluoroscopy and x-rays of the chest and heart (Fig. 2) suggested both right and left ventricular enlargement. The pulmonary artery segment was large, and there were prominent pulmonary vascular markings. The aorta appeared to be hypoplastic.

Cardiac catheterization was performed on June 17, 1952. During the procedure the catheter tip was passed through an interventricular septal defect and into the aorta (Fig. 2). The results of catheterization are shown in Table IV.

TABLE IV. FINDINGS ON CATHETERIZATION IN CASE 4

LOCATION	O_2 CONTENT c.c./100 c.c.	O_2 SATURATION (%)	PRESSURES, MM. HG S/D/MEAN
Superior vena cava	11.5	65	
Inferior vena cava	12.7	72	
Average venae cavae	12.1	69	
Right atrium	12.8	73	
Low right ventricle	13.9	79	
High right ventricle	14.3	81	52/0
Pulmonary artery	14.9	85	27/8/16
Aorta*	16.3	93	79/68
Femoral artery	16.2	93	96/66
O_2 capacity	17.6		

O_2 Consumption†	133 c.c./min.
Systemic flow	3.2 L./min.
Pulmonary flow‡	7.8 L./min.
L-R shunt	4.8 L./min.
R-L shunt‡	0.2 L./min.

*Catheter passed through ventricular septal defect.
†Estimated
‡Based upon an assumed 95% oxygen saturation of pulmonary vein blood.

Comment.—Moderate pulmonary stenosis has been demonstrated by the pressure tracings (Fig. 3) and an interventricular septal defect by the passage of the catheter through the defect. Here again there are a definitely increased pulmonary blood flow and an essentially normal pulmonic pressure in spite of the pulmonic stenosis.

It is of interest that only one of the four cases was diagnosed as having pulmonic stenosis prior to catheterization, although all had right ventricular enlargement and signs of pulmonic stenosis. The presence of a moderately loud pulmonic second sound was a source of confusion in two of the cases. This sign is readily explained, however, by the finding of high normal or slightly elevated pulmonary artery pressures.

With the exception of Case 2 who was diagnosed as a pure pulmonic stenosis and who had normal pulmonary vascular markings on chest x-ray, the finding of pulmonary plethora and in one instance (Case 1) the finding of a "hilar dance" at fluoroscopy definitely obscured the diagnosis for the clinician. The confusion brought about by such x-ray findings has been mentioned by other authors reporting on this situation.[2,6]

Since the flow of blood through the ventricular defect is dependent on a pressure differential between the right and left ventricles, there should in these cases be a lower right ventricular pressure than left. As seen in Table V the systolic pressures in the aorta (and therefore also the left ventricle) in Cases 2 and 4 are significantly higher than the pressures in the right ventricle. It has been shown that the peak systolic pressure is higher in the femoral artery than in the aorta due to the so-called "standing wave."[9] The difference as found in this laboratory and by Wood and associates[10] amounts to about 15 mm. Hg. Thus it can be seen that, even allowing for this difference, both of the other

TABLE V. PRESSURES IN THE RIGHT VENTRICLE, FEMORAL ARTERY, AND AORTA IN FOUR CASES OF PULMONIC STENOSIS WITH INTERVENTRICULAR SEPTAL DEFECT

	SYSTOLIC RIGHT VENTRICULAR PRESSURE (MM. HG)	SYSTOLIC FEMORAL ARTERY PRESSURE (MM. HG)	SYSTOLIC AORTIC PRESSURE (MM. HG)
Case 1	90	110	95*
Case 2	76	102	86†
Case 3	64	87	72*
Case 4	52	96	79†

*Estimated
†Determined

cases (1 and 3) have a systemic systolic pressure which exceeds the right ventricular systolic pressure. Broadbent and associates[3] found in five cases of pulmonic stenosis with interventricular septal defect and arteriovenous shunt only slight differences in pressure between the right ventricle and systemic arteries. They suggest, for no apparent reason, that this may be a characteristic of the syndrome and a means of distinguishing such lesions from atrial defects with pulmonary stenosis and arteriovenous shunts. Data from the four cases presented in this paper indicate that the level of the right ventricular pressure offers no indication as to the site of the septal defect in most cases with this condition. Only when the right ventricular pressure exceeds the left ventricular pressure and no arterial unsaturation is present can one assume the existence of an atrial defect instead of an interventricular defect. Furthermore, two of Broadbent's cases (6 and 9) showed no evidence of significantly increased pulmonary blood flow so that the pressures might have been expected to be almost equal. Case 6 may well have been an instance of pure pulmonic stenosis, since the calculated arteriovenous shunt was only 6 per cent; and in the other case, although the catheter passed through the defect, the right-to-left and left-to-right shunts were 17 per cent and 15 per cent, respectively, indicating a small mixed shunt with no net increase in pulmonary blood flow.

It is of further interest to examine the resistances involved in the outflow of blood from the right ventricle as compared to those of the left ventricle (Table VI). The values are determined by the formulas of Gorlin and Gorlin.[11] While the possible inaccuracies of these formulas are recognized, it seems worthwhile using them because they do give a crude indication of orifice size. The resistances of the pulmonary circuit are considerably lower than those of the systemic circuit thereby giving rise to the almost pure left-to-right shunt, mixing or other factors accounting for the very slight drop in arterial saturation in two of the cases. It is clear that the ventricular defects in these cases must be fairly small and the resistance of the defect itself to blood flow must be considerable, or the actual shunt would be larger than that observed.

TABLE VI. BLOOD FLOWS, RESISTANCES, AND PULMONARY VALVE AREAS IN FOUR CASES OF PULMONIC STENOSIS WITH INTERVENTRICULAR SEPTAL DEFECT

PULMONARY BLOOD FLOW (L./MIN.)	SYSTEMIC BLOOD FLOW (L./MIN.)	PULMONARY VALVE RESISTANCE (DYNES/SEC./CM.$^{-5}$)	PULMONARY VASCULAR RESISTANCE (DYNES/SEC./CM.$^{-5}$)	SYSTEMIC VASCULAR RESISTANCE (DYNES/SEC./CM.$^{-5}$)	PULMONARY VALVE AREA (SQ. CM.)
12.7	5.1	302	151	1390	1.6
7.0	4.1	490	137	1600	0.9
5.1	2.9	470	314	1905	0.7
7.8	3.2	246	164	2010	1.2

The figures for pulmonic valvular resistance and pulmonic valve area are also shown in Table VI. The valve areas are comparable to those found in pure pulmonic stenosis.[11] The valvular resistances (250 to 500 dynes/sec./cm.$^{-5}$) are also comparable to those found in pure pulmonic stenosis[8,11] (Fig. 4), most of which are considered to be stenoses of a relatively mild degree.[8] They are also comparable to the crudely calculated valvular resistances of three of the five similar cases reported by Broadbent and associates[3] (Fig. 4). It is of interest that the two cases of Broadbent and associates which showed high pulmonic valve resistances also showed no significant left-to-right shunt and no increased pulmonary blood flow.

These low pulmonic valve resistances are in striking contrast to the valvular resistances found in cases of tetralogy of Fallot[8,12] which ranged from 900 to 4,000 dynes/sec./cm.$^{-5}$ (Fig. 4). Although the present cases showed this marked difference, Broadbent's two cases and other cases in this laboratory suggest that there is a continuous range extending from the very mild stenoses (e.g., Case 4) with pure left-to-right shunt, through cases with mixed shunts, to very severe tight stenoses with only right-to-left shunts which are essentially examples of Fallot's tetralogy.

The lack of symptoms which the present cases and those of Broadbent and associates[3] showed seems consistent with the mild degree of pulmonic stenosis and the fact that the left-to-right shunt is only moderate. It may well be that in the absence of pulmonic stenosis pulmonary flow of blood would be still larger.

The pressing problem in these cases is whether or not surgery is indicated. It seems obvious that the most desirable surgery would be the repair of the interventricular septal defect with a subsequent pulmonary valvotomy if indicated. It may be that in the future this procedure can be done. For the present, the only question is whether or not a valvotomy should be done. For those individuals who show a large left-to-right shunt and increased pulmonary flow at rest, a successful valvotomy with reduction of pulmonic valve resistance would

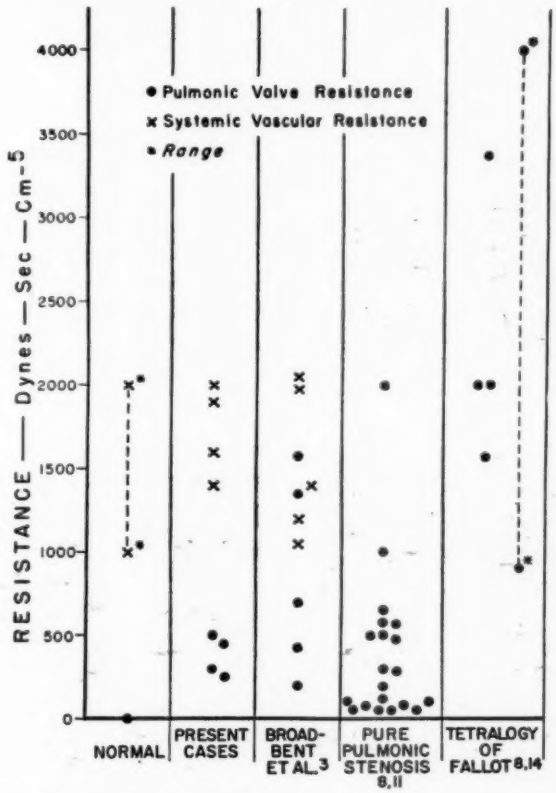


Fig. 4.—Chart showing pulmonary valvular resistances and systemic vascular resistances in cases of pulmonic stenosis with interventricular septal defect and left-to-right shunt, in cases of pure pulmonic stenosis, and in cases of Fallot's tetralogy.

perhaps only increase this flow; therefore, these individuals should be left alone until septal surgery is available. Individuals with a small left-to-right shunt and only slightly increased pulmonic flow at rest may, because of the relatively fixed resistance and orifice of the pulmonary valve, show a reversal of the shunt upon exercise. If a successful valvotomy be done it may cause some increased pulmonary flow at rest, but at the same time allow exercise to be performed without arterial unsaturation. Broadbent and associates[3] report one such case who received apparent benefit.

INTERATRIAL SEPTAL DEFECTS

CASE 5.—F. K. This 25-year-old unmarried woman entered Stanford University Hospital on May 23, 1949. A heart murmur had been discovered at the age of 4 years. She had developed normally and had been free of symptoms.

Physical examination revealed a healthy-appearing woman. There was a prominent systolic thrill in the pulmonic area, and a loud systolic murmur was heard in the same area. A loud pulmonic second sound was present.

The erythrocytes were 4.4 million/c.mm., the hemoglobin was 14.0 grams/100 c.c., and the hematocrit was 46 per cent.

The electrocardiogram was compatible with right ventricular hypertrophy (Fig. 5*A*).

X-ray and fluoroscopy of the chest and heart (Fig. 6) showed right ventricular enlargement, a markedly enlarged pulmonary artery segment which showed vigorous pulsation, and abnormally prominent pulmonary vascular markings. The aorta was thought to be hypoplastic.

She was catheterized on May 25, 1949. During the procedure the catheter tip passed through an atrial septal defect into the left atrium (Fig. 6). The results of the study are shown in Table VII.

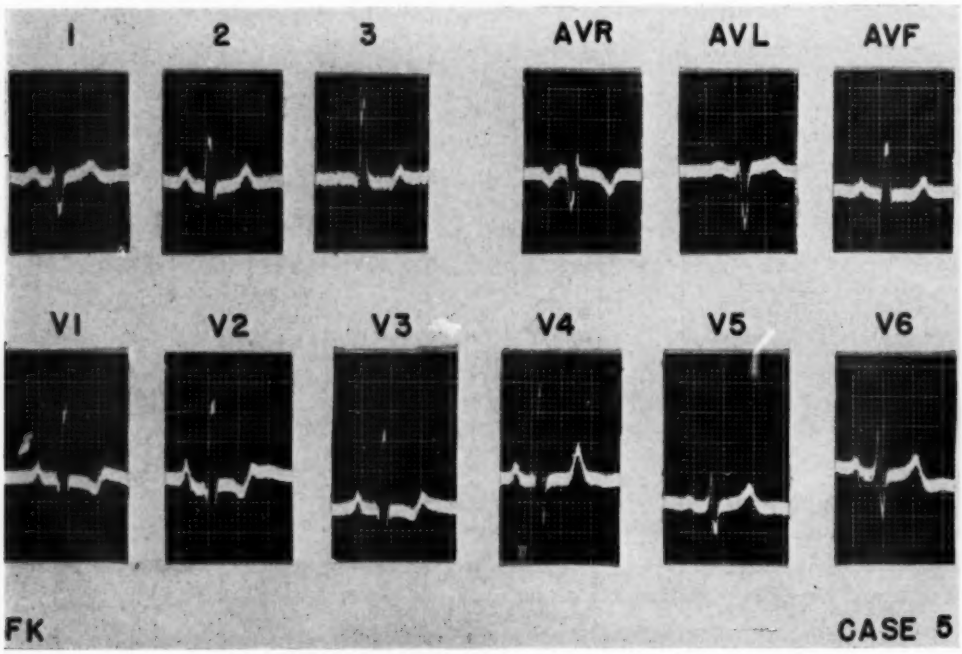


Fig. 5*A*.

Fig. 5.—*A* and *B*. Electrocardiograms in the three cases of pulmonic stenosis with interatrial septal defect.

Comment.—Although some of the signs of pulmonic stenosis were present in this case, the presence of a loud pulmonic second sound and pulmonary plethora obscured this diagnosis. Cardiac catheterization clearly demonstrated the presence of pulmonic stenosis (Fig. 7) and an atrial septal defect with increased pulmonary flow. The rather high pulmonary artery pressure (41/13 mm. Hg) explains the loud second pulmonic sound and pulmonary artery pulsation.

This patient was recatheterized in April, 1954, in another laboratory where similar findings were noted and the same diagnosis made. In May, 1954, her atrial septal defect was closed by Dr. Robert Gross of Boston. She has subsequently improved but a systolic murmur, suggestive of pulmonic stenosis, is still present in the pulmonic area.

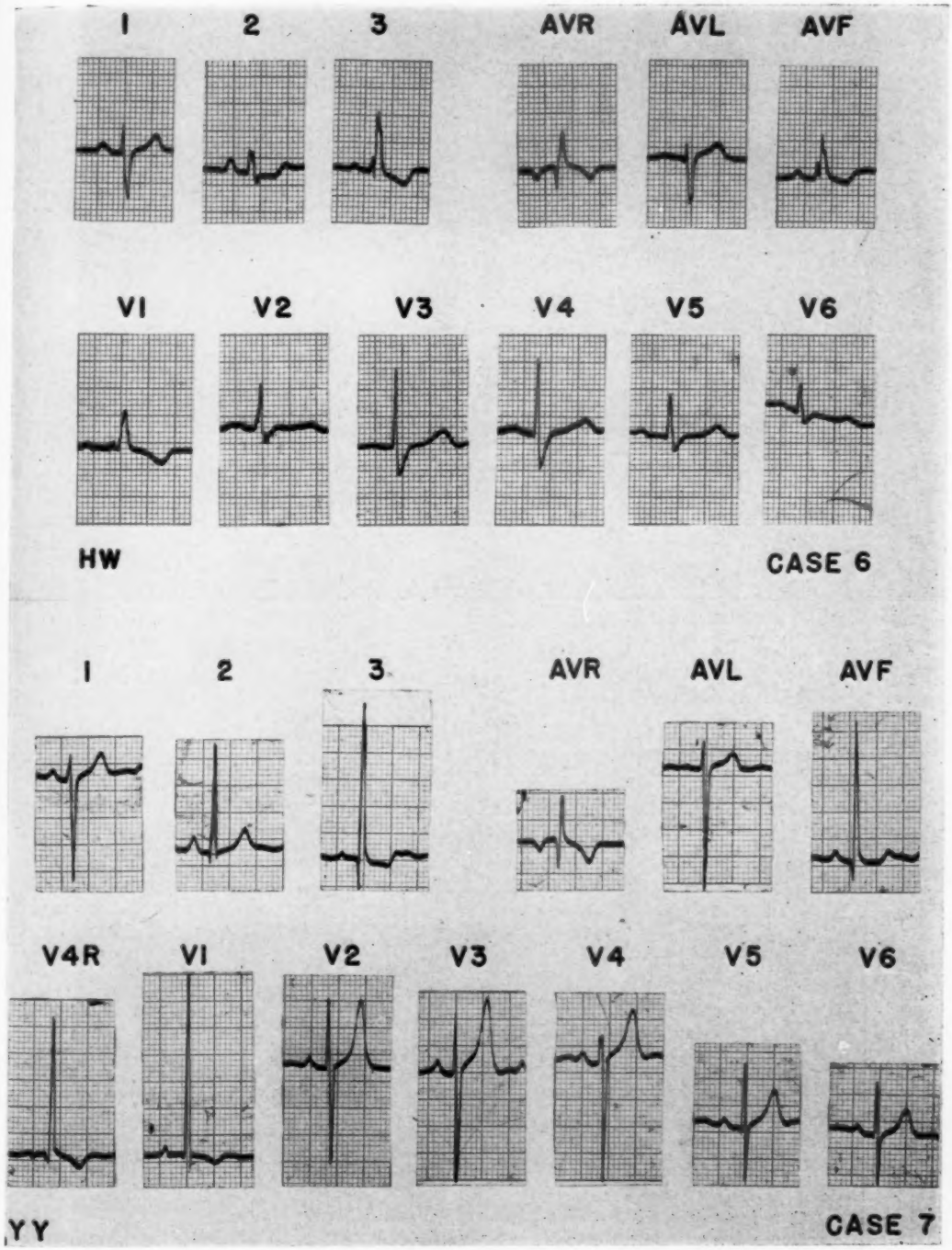


Fig. 5B. *(For legend see opposite page.)*

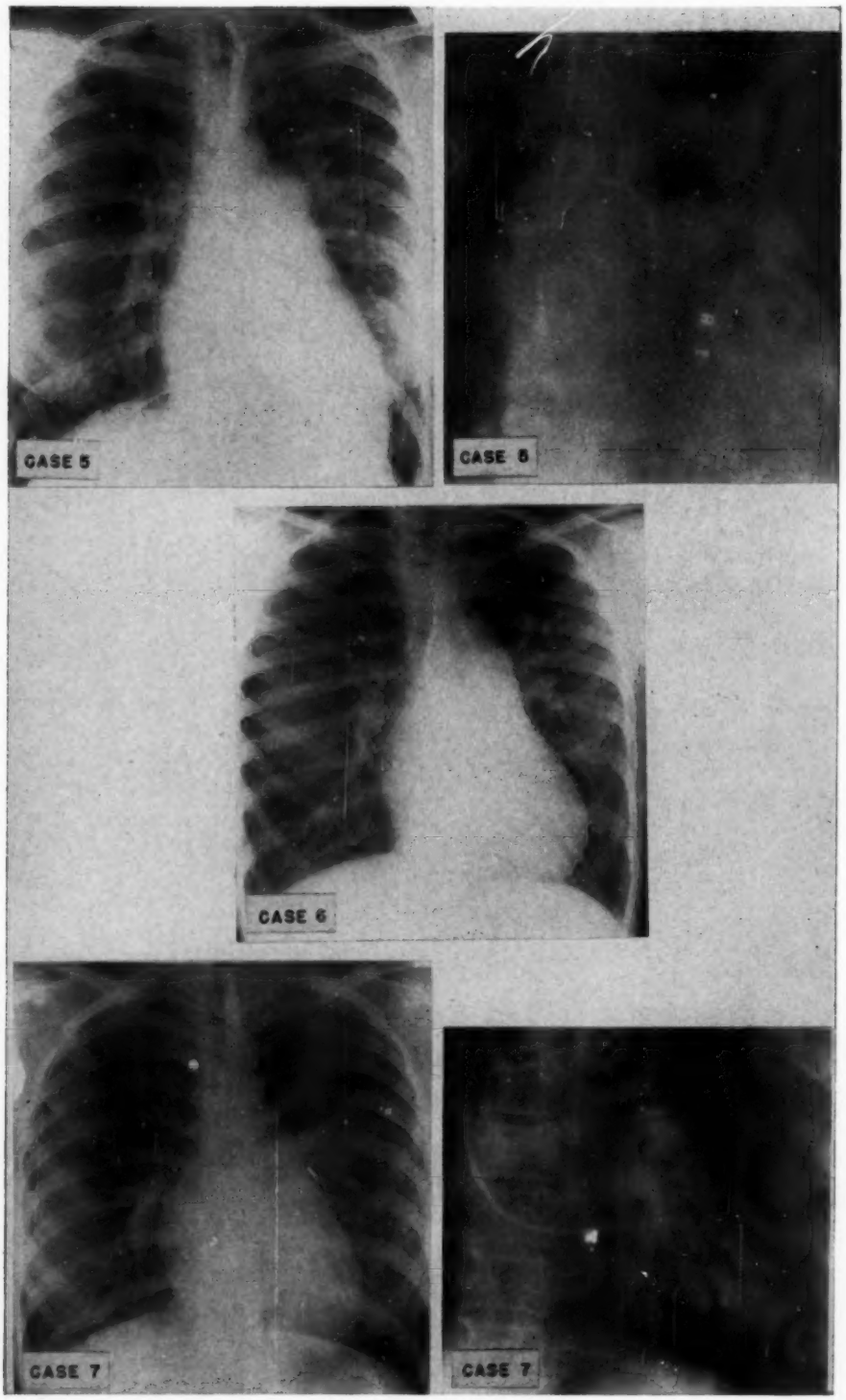


Fig. 6.—Chest x-rays in three cases of pulmonic stenosis with interatrial septal defect. Films taken at cardiac catheterization in Cases 5 and 7 show catheter in left atrium.

TABLE VII. FINDINGS ON CATHETERIZATION IN CASE 5

LOCATION	O_2 CONTENT (C.C./100 C.C.)	O_2 SATURATION (%)	PRESSURES, MM. HG S/D/MEAN
Superior vena cava	13.9	70	
Inferior vena cava	11.6	59	
Average venae cavae	12.8	65	
Right atrium	16.4	83	20/6/13
Right atrium	16.7	85	
Right ventricle	16.4	83	80/1
Pulmonary artery	16.0	81	41/13/26
Left atrium*	17.7	90	23/4/14
Brachial artery	17.8	90	120/70
O_2 capacity	19.7		

O_2 Consumption†	195 c.c./min.
Systemic flow	3.9 L./min.
Pulmonary flow‡	8.5 L./min.
L-R shunt	5.3 L./min.
R-L shunt‡	0.7 L./min.

*Catheter passed through atrial septal defect.
†Determined
‡Based upon an assumed 95 per cent oxygen saturation of pulmonary vein blood.

CASE 6.—H. W. This 14-year-old white girl entered Stanford University Hospital on July 19, 1953. Shortly after her birth, her parents were told that she had "heart trouble." Her only symptom had been dyspnea on exertion " . . . for as long as I can remember," and her activities had been somewhat limited by this.

Physical examination revealed a healthy-appearing well-developed young girl. Blood pressure in the right arm was 132/80 mm. Hg, in the leg 150/100 mm. Hg. A slight left precordial bulge was noted. There was an easily felt systolic thrill in the second left intercostal space and a loud systolic murmur in the same area. The pulmonic second sound was moderately loud.

TABLE VIII. FINDINGS ON CATHETERIZATION IN CASE 6

LOCATION	O_2 CONTENT C.C./100 C.C.	O_2 SATURATION (%)	PRESSURES, MM. HG S/D/MEAN
Superior vena cava	12.4	64	
Inferior vena cava	14.4	75	
Average venae cavae	13.4	69	
Right atrium	16.9	88	–/–/4
Right atrium	16.7	87	
Right ventricle	17.0	88	71/11
Pulmonary artery	17.0	88	–/–/17
Femoral artery	18.0	93	106/68
O_2 capacity	19.3		

O_2 Consumption*	209 c.c./min.
Systemic flow	4.5 L./min.
Pulmonary flow†	16.1 L./min.
L-R shunt	11.9 L./min.
R-L shunt†	0.3 L./min.

*Determined.
†Based upon an assumed 95 per cent oxygen saturation of pulmonary vein blood.

The hemoglobin was 16.3 grams/100 c.c., and the hematocrit was 47 per cent.

The electrocardiogram (Fig. 5*B*) was compatible with right ventricular hypertrophy and an incomplete right bundle branch block.

X-rays and fluoroscopy of the heart and chest (Fig. 6) revealed an enlarged right ventricle with a very prominent pulmonary artery segment. The peripheral pulmonary vessels were also quite prominent. The aorta was thought to be hypoplastic.

Cardiac catheterization was performed on July 21, 1953. The results are shown in Table VIII.

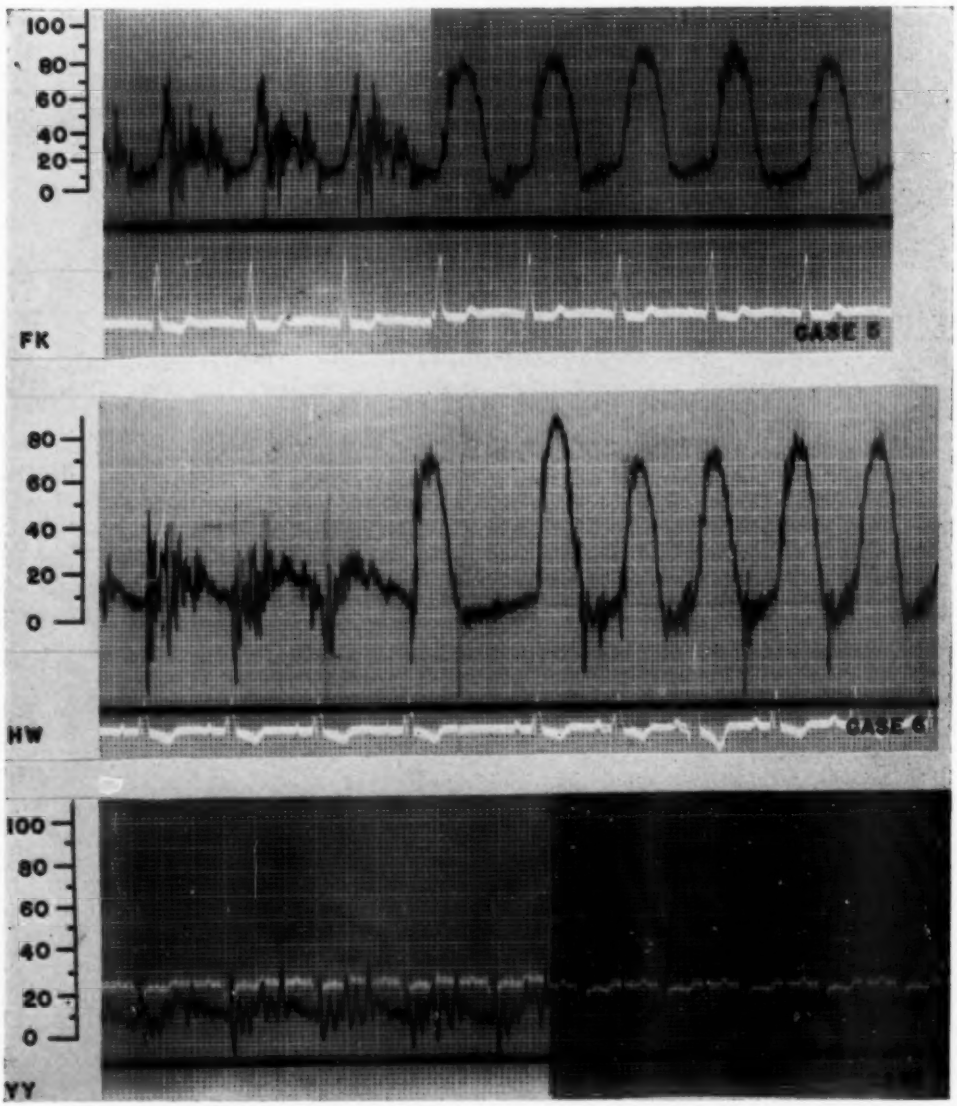


Fig. 7.—Pressure tracings from the pulmonary artery (left of each tracing) and right ventricle (right of each tracing) in three cases of pulmonic stenosis with interatrial septal defect.

Comment.—The very large pulmonary flow due to the left-to-right shunt through the atrial defect explains the finding of pulmonary plethora on the x-ray in spite of a moderately severe pulmonary stenosis (Fig. 7).

CASE 7.—Y. Y. This 14-year-old Japanese schoolgirl entered Stanford University Hospital on Nov. 8, 1950. She had been found to have a heart murmur at the age of 4½ years when she was examined because of measles. She had been diagnosed as having rheumatic fever at the age of 13, on the basis of frequent upper respiratory infections, fever, and pains in the knees on walking, but she had never had any demonstrable arthritis. She was asymptomatic except for occasional palpitation upon exercise.

Physical examination revealed a healthy-appearing young girl. Blood pressure in the arm was 108/70 mm. Hg, in the leg 120/78 mm. Hg. Her pulse rate was 88. There was a prominent systolic thrill and a loud systolic murmur maximal in the second left intercostal space. The pulmonary component of the second sound was soft.

The erythrocytes were 3.9 million/c.mm., the hemoglobin was 13.7 grams/100 c.c., and the hematocrit was 41 per cent.

The electrocardiogram (Fig. 5*B*) was compatible with right ventricular hypertrophy.

Fluoroscopy and x-rays of the chest and heart (Fig. 6) showed right ventricular enlargement, a prominent pulmonary artery segment, and increased pulmonary vascular shadows. The aorta was thought to be hypoplastic.

Cardiac catheterization was performed on Nov. 13, 1950. During the procedure the catheter tip passed through an atrial septal defect into the left atrium (Fig. 6). The results of catheterization are shown in Table IX.

TABLE IX. FINDINGS ON CATHETERIZATION IN CASE 7

LOCATION	O_2 CONTENT C.C./100 C.C.	O_2 SATURATION (%)	PRESSURES, MM. HG S/D/MEAN
Superior vena cava	12.5	67	
Inferior vena cava	12.5	67	
Average venae cavae	12.5	67	
Right atrium	14.6	79	-/-/6
Right ventricle	15.3	83	94/9
Pulmonary artery	15.4	83	-/-/12
Left atrium*	17.2	93	-/-/9
Femoral artery	17.0	92	120/78†
O_2 capacity	18.5		

O_2 Consumption‡	195 c.c./min.
Systemic flow	4.3 L./min.
Pulmonic flow§	8.9 L./min.
L-R shunt	5.1 L./min.
R-L shunt§	0.5 L./min.

*Catheter passed through atrial septal defect.
†Cuff measurement.
‡Determined.
§Based upon an assumed pulmonary vein oxygen saturation of 95%.

Comment.—Cardiac catheterization showed the presence of a pulmonic stenosis (Fig. 7) and an atrial septal defect with increased pulmonary blood flow.

Although all three of these patients showed definite signs of pulmonic stenosis, the diagnosis was confused because of the evidence of increased pulmonary blood flow seen on the x-rays. It has been noted before that there is a slight pressure differential between right ventricle and pulmonary artery in cases of atrial septal defect,[13,14] and it has been suggested that a relative stenosis of the pulmonic valve ring due to dilatation of the pulmonary artery conus may be the cause of the systolic murmurs in atrial septal defects.[15] That a true pulmonic stenosis is present in the three cases reported in this paper can be seen from the

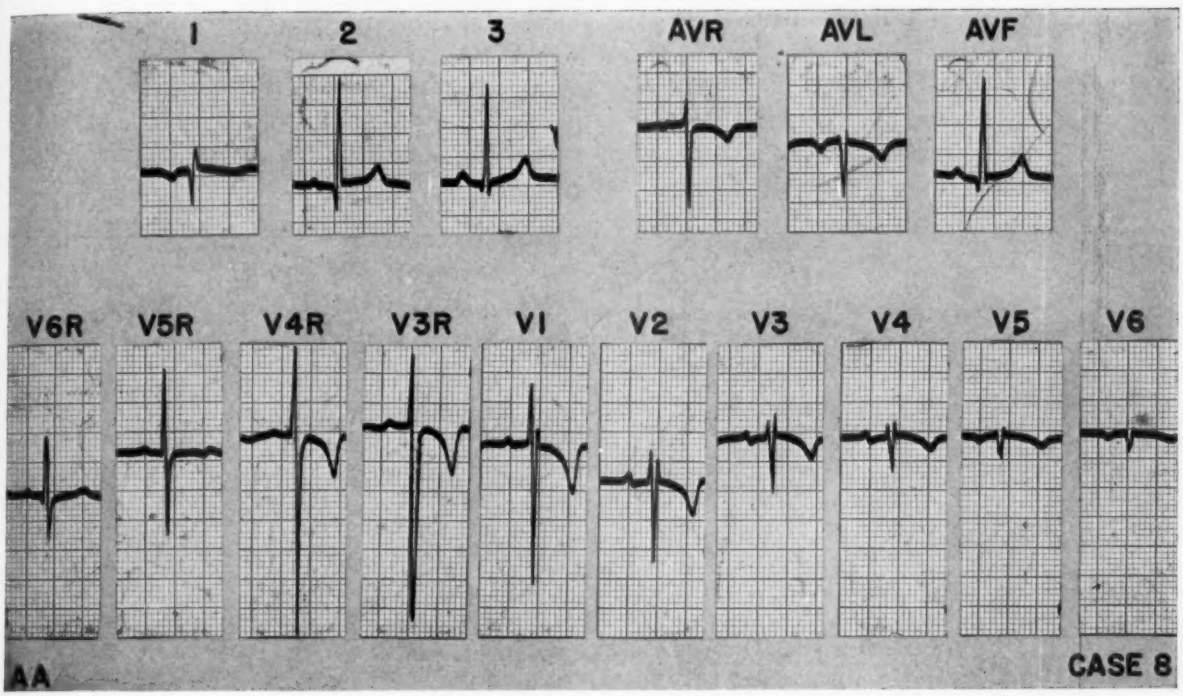
high right ventricular pressure and large size of the right ventricular-pulmonary artery pressure gradient. The pulmonary valve resistances and valve areas (Table X) are comparable to those found in the cases with ventricular defects and are consistent with a moderate degree of stenosis. This is compatible with the lack of severe symptoms or disability.

TABLE X. BLOOD FLOWS, RESISTANCE, AND PULMONIC VALVE AREAS IN THREE CASES OF PULMONIC STENOSIS WITH INTERATRIAL SEPTAL DEFECT

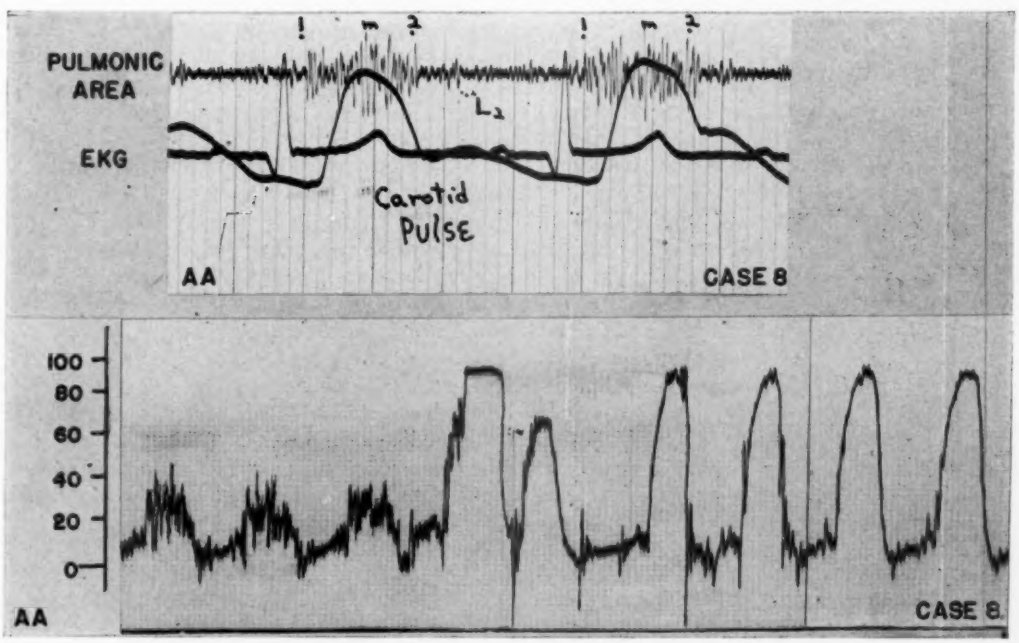
	PULMONARY BLOOD FLOW (L./MIN.)	SYSTEMIC BLOOD FLOW (L./MIN.)	PULMONARY VALVE RESISTANCE (DYNES/SEC./CM.$^{-5}$)	PULMONARY VASCULAR RESISTANCE (DYNES/SEC./CM.$^{-5}$)	PULMONARY VALVE AREA (SQ. CM.)
Case 5	8.5	3.9	348	244	1.3
Case 6	16.1	4.5	209	85	1.9
Case 7	8.9	4.3	475	108	0.9

It should be apparent that the mechanism which affects the direction of shunt in these cases is different from that in ventricular septal defects with pulmonic stenosis. As shown before, the shunt in the latter is dependent upon the relative pressures in the ventricles and upon the resistance to outflow imposed by the stenosed pulmonary valve as compared to the systemic resistance. In atrial defects the direction of the shunt is dependent upon the relative pressures in the two auricles and upon the resistances to outflow from the auricles.[14] Since the pulmonic valve is closed normally whenever the A-V valves are open, it is clear that the degree of stenosis of the pulmonic valve has no direct relationship to the resistance to outflow from the auricle and therefore no direct relationship to direction or degree of shunt. Hull[16] has discussed the following factors which do affect the resistance to auricular outflow: (1) the smaller size of the mitral orifice as compared to the tricuspid, (2) the longer and narrower left ventricle as compared to the right ventricle, (3) the less efficient operation of the mitral valve as compared to the tricuspid, (4) the thicker and less distensible walls of the left ventricle as compared to the right, and (5) the presence of decompensation with decreased distensibility of one or the other ventricle. It is thus obvious that pulmonic stenosis can affect the resistance to right auricular outflow only indirectly, as it influences (1) right ventricular hypertrophy with increased resistance to distention, and (2) development of ventricular decompensation. It can therefore be readily understood that a mild stenosis is likely to be accompanied by a left-to-right atrial shunt, and a more severe stenosis with a right-to-left shunt. The experimental work of Brecher and Opdyke[17] supports this view. It seems quite probable that in the atrial defects, as in the ventricular defects with pulmonic stenosis, there is a continuous range from cases with pure left-to-right shunt to those with a pure right-to-left shunt and cyanosis. The latter condition has been described by a number of authors.[18-20]

Surgery in this condition would, as in the ventricular defects, ideally be aimed at closure of the atrial septal defect, and relief of the pulmonic stenosis



A.



B;

C;

Fig. 8.—Tracings in case of aortic-pulmonary artery communication with pulmonic stenosis. *A*, 16-lead electrocardiogram showing situs inversus. *B*, Phonocardiogram with Lead II electrocardiogram and carotid pulse. *C*, Pressures in pulmonary artery (left side of tracing) and right ventricle (right side of tracing).

if necessary. A pulmonary valvotomy alone would cause an increased pulmonary blood flow if, as a result of the surgery, resistance to right ventricular filling were decreased. If ventricular resistance to filling were unchanged by operation, it is also conceivable that there would be no effect on pulmonary flow. There has been no reported result of pulmonary valvotomy in a case with atrial defect and increased pulmonary flow.

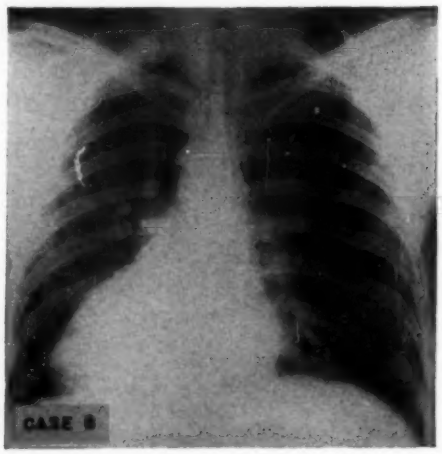


Fig. 9.—Chest x-ray in case of aortic-pulmonary artery communication with pulmonic stenosis and situs inversus.

AORTIC-PULMONARY COMMUNICATION

CASE 8.—A. A. This 33-year-old man entered Stanford University Hospital on March 19, 1952, with a complaint of dyspnea for several years. He had suffered from "blue spells" as a baby, and a heart murmur had been noted at the age of 2 years. However, he had been very active as a child and had engaged in athletics in high school. Ten years prior to entry he had received a thorough examination and had been found to have only a systolic murmur at the cardiac base. For about three years he had noted increasing fatigue and exertional dyspnea, and about one year before entering the hospital he had experienced an episode of hemoptysis and fever.

Physical examination revealed a husky healthy-appearing man. The peripheral pulse was quite full. The pulse rate was 80. The blood pressure in the arm was 110/55 mm. Hg. The heart was on the right side of the chest. A continuous murmur was heard in the second intercostal space to the right of the sternum. At the third and fourth intercostal spaces along the right sternal border the systolic component of the murmur was very loud. The aortic component of the second sound was loud and the pulmonic component was absent.

The hemoglobin was 19.1 grams/100 c.c. and the hematocrit was 54 per cent.

The electrocardiogram was compatible with a complete situs inversus (Fig. 8, *A*) and in addition, showed inversion of the T waves across the precordium to Lead V5R. A phonocardiogram (Fig. 8, *B*) revealed a continuous murmur in the right second intercostal space with a very loud systolic component.

Fluoroscopy and x-rays of the chest and heart (Fig. 9) showed complete situs inversus. There were systemic (normal left) ventricular enlargement, marked pulmonary vessel engorgement, and considerable pulsation of the pulmonary vessels.

Cardiac catheterization was performed on March 20, 1952. The results are shown in Table XI.

Comment.—Catheterization suggested the presence of a patent ductus arteriosus with significantly increased pulmonary flow, in addition to a definite pulmonic stenosis (Fig. 8,*C*). However, surgery done on April 1, 1952, revealed

TABLE XI. FINDINGS ON CATHETERIZATION IN CASE 8

LOCATION	O_2 CONTENT (C.C./100 C.C.)	O_2 SATURATION (%)	PRESSURES, MM. HG S/D/MEAN
Superior vena cava	15.8	62	
Inferior vena cava	15.1	60	
Average venae cavae	15.5	61	
Right atrium	15.4	61	
Right ventricle	15.7	62	85/8
Pulmonary artery	20.7	82	28/6
Femoral artery	24.3	96	118/54
Exercise			
Right ventricle	13.5	53	100/8
Pulmonary artery	20.4	80	43/28
Femoral artery	24.3	96	160/65
O_2 capacity	25.4		

	Rest	*Exercise*
O_2 consumption*	242 c.c./min.	452 c.c./min.
Systemic flow	2.8 L./min.	4.2 L./min.
Pulmonary flow	6.7 L./min.	11.6 L./min.
L-R shunt	3.9 L./min.	7.4 L./min.

*Determined

a nonpatent fibrous ductus arteriosus and evidence of a thrill in the most proximal part of the pulmonary artery. The findings were felt to be consistent with a diagnosis of aortic-pulmonic septal defect. In view of this man's history and prior finding of only a systolic murmur it was felt that the defect had been acquired, perhaps by a rupture of a sinus of Valsalva aneurysm into the pulmonary artery.

The hemodynamic effect of such a lesion is much the same as that due to a patent ductus arteriosus, with increased pulmonary blood flow and a high normal pulmonary artery pressure.

Obviously, a pulmonary valvotomy here would only increase further the pulmonary flow and would be contraindicated for that reason. The procedure of choice would be a closure of the septal defect.

DISCUSSION

The possible conditions in association with pulmonic stenosis which show increased pulmonary blood flow are essentially the same as those which show increased pulmonary flow in the absence of pulmonic stenosis. These have been previously discussed by Deuchar and Zak.[2]

Since atrial and ventricular septal defects are the commonest defects associated with increased pulmonary flow, one would also expect them to be the commonest causes of increased pulmonary flow when associated with pulmonic stenosis. That this is true can be seen from the fact that most of the cases reported with this combination of findings have been associated with atrial or ventricular defects,[3-6,8] only a few having anomalous venous return,[2] aortic-pulmonary,[1,2,7] or aortic-right ventricle communications.[2,6] Case 2 of Deuchar and Zak[2] which was classified as an example of anomalous venous return would

also be compatible with an interatrial septal defect plus pulmonic stenosis and a left-to-right shunt.

The main problem in most of these combinations of defects has been the diagnosis of the pulmonic stenosis. The prominence of the pulmonary vascular markings on x-ray, indicating a left-to-right shunt, and the presence of a loud pulmonic second sound have often been factors in causing a pulmonic stenosis to be overlooked in spite of other physical findings suggesting its presence. These physical signs are the typical harsh systolic murmur heard in the pulmonary area to the left of the sternum and beginning after the first heart sound, a systolic thrill in the same area, and a right ventricular heave. In addition to the physical signs of pulmonic stenosis, the finding of a right ventricular hypertrophy pattern, in contrast to the normal or incomplete right bundle branch block patterns of uncomplicated septal defects, should be helpful in suggesting the coexistence of pulmonic stenosis. Certain of the cases which have only a moderate stenosis and a very large pulmonary blood flow probably can be diagnosed with certainty only at cardiac catheterization.

The mild physical symptoms found in this group of patients are compatible with the moderate degree of pulmonic stenosis. A stenosis severe enough to give symptoms would in all probability also cause a reversal of shunt and cyanosis.

SUMMARY

1. Eight cases of pulmonic stenosis with increased pulmonary blood flow have been described. Four cases had an interventricular septal defect, three an atrial septal defect and one, an aortic-pulmonary artery communication.

2. Such cases are not rare since they occur at least as frequently as instances of Eisenmenger's syndrome.

3. The essential clinical features consist of a combination of the signs of an atrial or an interventricular septal defect associated with those of a pulmonic stenosis. Increased pulmonary vascular markings which are seen by x-ray caused the pulmonic stenosis to be overlooked in seven of the above eight cases. In five cases the pulmonic second sound was accentuated.

4. Surgery should be directed toward closure of the septal defect where this is possible since the degree of pulmonic stenosis is usually mild and further enlargement of the valve orifice may only increase the magnitude of the left-to-right shunt.

SUMMARIO IN INTERLINGUA

1. Es describite octo casos de stenosis pulmonar con augmentate fluxo de sanguine pulmonar. Quatro del casos habeva un defecto septal interventricular; tres casos habeva un defecto septal atrial; e un caso un communication inter aorta e arteria pulmonar.

2. Casos de iste genere non es rar. Illos occurre al minus tanto frequentemente como le syndrome de Eisenmenger.

3. Le characteristicas clinic essential consiste de un combination del signos de un defecto septal (atrial o interventricular) con illos de un stenosis pulmonar. Un augmento del marcas vascular pulmonar que se vide in le roentgenogramma esseva responsabile in septe del octo casos pro le facto que le stenosis pulmonar

non esseva constatate. In cinque del casos le secunde sono pulmonar esseva accentuate.

4. Le objectivo del intervention chirurgic in tal casos debe esser, in tanto que possibile, le clausura del defecto septal, proque le grado del stenosis pulmonar es generalmente leve e un allargamento additional del orificio valvular pote solmente resultar in un augmento del derivation ab le sinistra verso le dextera.

ADDENDUM

Since this paper was submitted for publication, three additional cases of pulmonic stenosis with increased pulmonary blood flow have been studied in our laboratory. In each case there was a coexistent atrial septal defect. Case 1 described in this paper has been restudied eight months after closure of the atrial septal defect. The patient is now asymptomatic, and all evidence of the presence of the prominent atrial defect has disappeared. However, there is still present, after exercise, a faint but distinct systolic murmur at the pulmonic area which is initiated by an opening snap indicating the presence of a mild pulmonic stenosis.

Meanwhile, two excellent additional studies of this problem have been published[1,2] expressing conclusions essentially similar to ours.

1. Magidson, O., Cosby, R. S., Dimitroff, S. P., Levinson, D. C., and Griffith, G. C.: Pulmonary Stenosis With Left to Right Shunt, Am. J. Med. **17**:311, 1954.
2. Rudolph, A. M., Nadas, A. S., and Goodale, W. T.: Intracardiac Left-to-right Shunt With Pulmonic Stenosis, AM. HEART J. **48**:808, 1954.

REFERENCES

1. Taylor, B. E., and DuShane, J. W.: Patent Ductus Arteriosus Associated With Pulmonary Stenosis, Proc. Staff. Meet., Mayo Clin. **25**:60, 1950.
2. Deuchar, D. C., and Zak, G. A.: Cardiac Catheterization in Congenital Heart Disease. I. Four Cases of Pulmonary Stenosis With Increased Pulmonary Blood Flow. Guy's Hosp. Rep. **101**:1, 1952.
3. Broadbent, J. C., Wood, E. H., and Burchell, H. B.: Left to Right Intracardiac Shunts in the Presence of Pulmonary Stenosis, Proc. Staff. Meet., Mayo Clin. **28**:101, 1953.
4. Moffitt, G. R., Zinsser, H. F., Jr., Kuo, P. T., Johnson, J., and Schnabel, T. G., Jr.: Pulmonary Stenosis With Left to Right Intracardiac Shunts, Am. J. Med. **16**:521, 1954.
5. Gøtzsche, H.: Congenital Heart Disease, Copenhagen, 1952, Publ. by author.
6. Wood, P.: Congenital Heart Disease, Brit. M. J. **2**:639; **2**:693, 1950.
7. Dexter, L.: Cardiac Catheterization in the Diagnosis of Congenital Heart Disease, Bull. New York Acad. Med. **26**:93, 1950.
8. Dow, J. W., Levine, H. D., Elkin, M., Haynes, F. W., Hellems, H. K., Whittenberger, J. W., Ferris, B. G., Goodale, W. T., Harvey, W. P., Eppinger, E. C., and Dexter, L.: Studies of Congenital Heart Disease. IV. Uncomplicated Pulmonic Stenosis. Circulation **1**:267, 1950.
9. Hamilton, W. F., and Dow, P.: An Experimental Study of the Standing Waves in the Pulse Propagated Through the Aorta, Am. J. Physiol. **125**:48, 1939.
10. Wood, E. H., Fuller, J., and Clagett, O. T.: Intraluminal Pressures Recorded Simultaneously From Different Arteries in Man, Am. J. Physiol. **167**:838, 1951.
11. Gorlin, R., and Gorlin, S. G.: Hydraulic Formulae for Calculation of the Area of the Stenotic Mitral Valve, Other Cardiac Valves, and Central Circulatory Shunts, AM. HEART J. **41**:1, 1951.
12. Unpublished observations.
13. Blount, S. G., Jr.: Personal communication.
14. Unpublished observations.
15. Cossio, P., Arana, R., Berconsky, I., and Kreutzer, R.: Congenital cardiopathias; diagnostic clinic, Sémana méd. **2**:364, 1938.
16. Hull, E.: The Cause and Effects of Flow Through Defects of the Atrial Septum, AM. HEART J. **38**:350, 1949.
17. Brecher, G. A., and Opdyke, D. F.: The Relief of Acute Right Ventricular Strain by the Production of an Interatrial Septal Defect, Circulation **4**:496, 1951.
18. Coelho, E., Da Fonseca, M., Pinto, R., and Nunes, A.: Pulmonary Stenosis With Large Interatrial Septum Defect and Severe Cyanosis, Cardiologia **18**:183, 1951.
19. Adams, F. H., Veasy, L. G., Jorgens, J., Diehl, A., LaBree, J. W., Shapiro, M. J., and Dwan, P. F.: Congenital Valvular Pulmonary Stenosis With or Without an Interatrial Communication, J. Pediat. **38**:431, 1951.
20. Loogen, F., Bayer, O., and Wolter, H. H.: Clinical and Physiologic Findings in Congenital Pulmonary Valvular Stenosis With or Without Atrial Septal Defect, Ztschr. Kreislaufforsch. **42**:115, 1953.

THE PHYSIOLOGICAL AND CLINICAL CHANGES FOLLOWING CLOSURE OF ATRIAL SEPTAL DEFECTS BY ATRIO-SEPTO-PEXY

HARRY GOLDBERG, M.D., AND DANIEL F. DOWNING, M.D.

PHILADELPHIA, PA.

ATRIAL septal defect, one of the most common of all congenital cardiac malformations, has been the subject of intensive investigation in recent years. The impression that this lesion is perfectly benign, with little consequence upon the cardiovascular system, has been largely dispelled by hemodynamic studies of the lesion by right-heart catheterization.[1,2] Although compatible with a relatively normal life span in some individuals, others may die early in infancy or childhood from congestive heart failure. Still others live to the third or fourth decade when they become disabled by progressive exertional dyspnea, fatigability, paroxysmal tachycardia, and congestive heart failure. The mean duration of life for patients with such lesions has been set at the mid-thirties. It became obvious that attempts to correct the malformation by surgical means must be made. Recently Bailey and associates[3] introduced a method of closure involving suturing of the right-atrial wall to the margin of the defect, terming the procedure atrio-septo-pexy. Since the original paper, much experience has been gained with the surgical treatment of these defects,[4] isolated and complicated by other lesions such as mitral stenosis and anomalous pulmonary venous drainage into the right atrium and/or superior vena cava.

The purpose of this communication is to present physiological and clinical data in a group of fifteen patients in whom follow-up hemodynamic studies have been possible following closure of the atrial septal defect. In two patients (J.S. and M.S.) with associated anomalous pulmonary venous drainage into the right atrium or superior vena cava, this has been accomplished by a modification of the original technique.[5]

METHODS OF STUDY

Atrio-septo-pexy as described by Bailey and associates[3] was performed in thirteen patients. One of these (R.B.) had a mitral commissurotomy as well. In two patients (M.S. and J.S.), a modification of the original technique was performed to include surgical correction of the anomalous pulmonary venous drainage as well as of the atrial septal defect.[5] The clinical data in all patients are found in Table I.

From the B'rith Sholom Cardiopulmonary Laboratory, Departments of Medicine and Pediatrics, Hahnemann Medical College and Hospital, and the Bailey Thoracic Clinic, Philadelphia, Pa.

Supported in part by the American Heart Association.

Presented at the Second World Congress in Cardiology, September, 1954, Washington, D. C.

Received for publication Sept. 7, 1954.

Cardiac catheterization was performed by the usual technique. The methods employed were described previously.[6] Pressures were measured with an electromanometer (Sanborn) with recordings on a direct polyoscillograph (Sanborn).

Blood samples were analyzed for oxygen content and capacity by the method of Van Slyke and Neill.[7] The oxygen content of expired gas was analyzed on the Pauling analyzer. The volume was expressed as dry gas at 0° C. and 760 mm. Hg.

Cardiac outputs were calculated by applying the Fick principle.

$$\text{Systemic blood flow (SBF)} = \frac{\text{Oxygen consumption}}{\text{BA} - \frac{(\text{SBC} + \text{IVC})}{(2)}}$$

$$\text{Pulmonic blood flow (PBF)} = \frac{\text{oxygen consumption}}{\text{PV} - \text{PA}}$$

$$\text{Effective* pulmonic blood flow (EPBF)} = \frac{\text{oxygen consumption}}{\text{PV} - \frac{(\text{SVC} + \text{IVC})}{(2)}}$$

BA = Brachial arterial oxygen content IVC = Inferior vena cava oxygen content
PV = Pulmonary venous oxygen content SVC = Superior vena cava oxygen content

If peripheral arterial oxygen saturation exceeded 92 per cent, which is considered normal for this laboratory, (92 to 100 per cent), the oxygen content of the peripheral blood was substituted for pulmonary venous blood. If the peripheral arterial blood oxygen saturation was below normal (due to contamination with venous blood by a right-to-left shunt), the pulmonary venous blood oxygen content was assumed to be 95 per cent of the blood oxygen capacity.

Evidence for a left-to-right shunt at the atrial level existed when the oxygen content of the right atrial blood samples exceeded the superior vena cava by more than 2 volumes per cent or the mean of the superior vena cava and inferior vena cava by 1.5 volumes per cent.[8]

Calculation of shunts:[9]

A. Total left-to-right (arteriovenous) shunt = PBF − EPBF
B. Total right-to-left (venoarterial) shunt = SBF − EPBF
C. Over-all shunt calculated from A and B

Pulmonary resistance (PR) and work of right ventricle:[10]

$$\text{Total pulmonary resistance (dynes/sec./cm.}^{-5}) = \frac{(\text{PA}_m - 0)}{\text{C. O. (c.c./sec.)}} \times 1332$$

$$\text{Work of the right ventricle} = \frac{(\text{PFI} \times 1.055)\ \ (\text{PA}_m \times 13.6)}{1000} \text{ Kg. m./min.}$$

C. O. = Cardiac output
PA_m = Mean pulmonary arterial pressure in mm. Hg

$$\text{PFI} = \text{Pulmonary flow index} = \frac{\text{PBF}}{\text{Surface area (M}^2\text{ BS)}}$$

*Effective pulmonic blood flow is defined as that portion of the caval blood which passes through the pulmonary bed.

TABLE I. CLINICAL FINDINGS IN PATIENTS WITH ATRIAL SEPTAL

CASE	AGE	SEX	EXERCISE TOLERANCE	DYSPNEA	FATIGUE	PALPIT.	OTHER SYMPTOMS	HIST. OF FAILURE
C.F. Preop.	22	M	D	+	0	0	none	0
Postop., 1 year			N	0	0	0	none	
J.S. Preop.	11	F	D	+	+	0	sync. chest pain	0
Postop., 14 mo.			M. I.	0	M.D.	0	none	
M.S. Preop.	41	F	D	+	+	0	sync. orthop.	+
Postop., 1 year			I	D	M.D.	0	orthop. less	
R.B. Preop.	44	F	D	+	+	0	chest pain hemop.	+
Postop., 13 mo.			I	D		0	no hemop. chest pain	
J.C. Preop.	35	M	D	+	+	0	none	+
Postop., 5 mo.			NC	NC	NC	0	none	
T.S. Preop.	6	M	D	+	+	0	none	+
Postop., 8 mo.			M. I.	0	M.D.	0	none	
P.F. Preop.	38	F	D	+	+	+	none	−
Postop., 4 mo.			M. I.	M.D.	M.D.	0	none	
M.K. Preop.	24	F	D	+	−	+	none	0
Postop., 23 days			I	0	0	0	none	

DEFECTS BEFORE AND AFTER ATRIO-SEPTO-PEXY

CONG. HT. DIS. (YR.)	THORACIC ASYMMETRY	CARDIAC FINDINGS				SIGNS OF FAILURE	ECG	X-RAY (CARDIAC CHAMBER ENLARGEMENT)
		THRILL	MURMUR		P_2			
			SYST.	DIAST.				
birth	—	0	+	0	2+	0	NSR RHS	RV 2+ PVM 2+ PA 3+
		0	0	0	2+	0	NSR RHS	NC
3 — 12	+	+	+	+	N	0	NSR RHS	Heart 2+ PVM 2+ PA 2+
		0	0	0	1+	0	NSR RHS	Heart N PVM ? incr.
30	—	0	+	0	I	0	WNL	PVM 1+
		0	1+	0	N	0	WNL	PVM N
at surgery	—	0	+	mid-apex	2+	0	NSR RHS	RV 2+ PVM 2+ PA 1+ RA 1+
		0	D	mid-apex	2+	0	NSR RHS	Heart decreased 1+ in mass.
1	—	—	+	0	2-3+	0	NSR with VPS + RHS	RV 2+ PVM 3+ Pa 4+
		0	+	early	2-3+	0	NSR no VPS + RHS	Heart size larger.
3	0	0	+	mid-apex	I	0	NSR RHS	RV 1+ PVM 3+ PA 2+
		0	0	0	N	0	—	MPA and PVM's less promin.
birth	—	—	4+	0	I	0	NSR RHS	RV 2+ PVM 2+ PA 3+
			1+	0	D	0	—	Less enl. to Rt. PA & PVM still increased.
21	0	0	+	pre-syst.	2+	0	WNL	RV 1+ PVM 2+ PA 2+ RA 1+
			0	0	1+	0	WNL	RV 1+ PVM N PA 2+

TABLE I. CLINICAL FINDINGS IN PATIENTS WITH ATRIAL SEPTAL

CASE	AGE	SEX	EXERCISE TOLERANCE	DYSPNEA	FATIGUE	PALPIT.	OTHER SYMPTOMS	HIST. OF FAILURE
J.B. Preop.	22	F	D	0	+	0	none	0
Postop., 7 mo.			I	0	0	0	none	
A.C. Preop.	17	M	D	+	+	−	orthop.	0
Postop., 7 mo.			M. I.	0	0	0	0	
C.S. Preop.	18	M	D	+	+	0	none	0
Postop., 8 mo.			I	D	D	0	none	
G.S. Preop.	42	F	D	+	+	+	none	+
Postop., 3 mo.			M. I.	M.D.	M.D.	0	none	
N.H. Preop.	27	F	D	+	+	occ.	sync.	0
Postop., 3 mo.			M. I.	0	M.D.	0	none	
H.W. Preop.	34	F	D	+	+	+	chest pain hemop.	+
Postop., 4 mo.			M. I.	M.D.	M.D.	0	none	
G.C. Preop.	51	F	−	0	0	+	chest pain	−
Postop., 14 mo.			−	0	0	0	none	

KEY: N = normal
+ = present
0 = absent
− = not mentioned
D = decreased
M.D. = markedly decreased
I = increased
Imp. = improved
M. Imp. = markedly improved
N.C. = no change
M. I. = markedly increased
Sync. = syncope

DEFECTS BEFORE AND AFTER ATRIO-SEPTO-PEXY (CONT'D)

CONG. HT. DIS. (YR.)	THORACIC ASYMMETRY	CARDIAC FINDINGS				SIGNS OF FAILURE	ECG	X-RAY (CARDIAC CHAMBER ENLARGEMENT)
		THRILL	MURMUR		P_2			
			SYST.	DIAST.				
5	—	0	+	0	2+	0	RBBB NSR	RV 1+ PVM 2+ PA 2+
		0	0	0	0-1+	0	NSR WNL	RV & PA NC PVM 0-1+
13	+	—	2+	0	2+	0	NSR RHS	RV 2+ PVM 2+ PA 2+ RA 1+
		0	1+	0	0-1+	0	Compl. A-V block	RV 1+ PVM N PA 2+
13	—	0	+	0	I	0	NSR RBBB incom.	RV 3+ PVM 1+ PA 3+
		0	+	0	I	0	NSR RBBB incom.	NC
37	—	0	+	0	3+	0	NSR APS RHS	RV 4+ PVM 3+ PA 3-4+ RA ↑ ?
		0	0	0	N	0	NSR RHS	RV 3+ PVM 1+ PA 2+
6	0	0	+	0	1+	0	RBBB	RV 1+ PVM 2+ PA 2+
		0	0	0	1-2+	0	RBBB	RV N PVM 1+ PA 1+
17	0	+	+	+	I	0	RHS	RV 3+ PVM 3+ PA 3+ RA 2+
		0	0	0	N	0	RHS	RV 1+ PVM 1+ PA 3+ RA N
13	0	0	+	0	2+	0	RBBB VPS 1° A-V block	RV 3-4+ PVM 3-4+ PA 3-4+
		0	0	0	N	0	RBBB	PA 2+ RV 1+ PVM 1-2+

Orthop. = orthopnea
Occ. = occasionally
NSR = normal sinus rhythm
RHS = right-heart strain
APS = atrial premature systoles
WNL = within normal limits
VPS = ventricular premature systoles
RBBB = right bundle branch block
PVM = pulmonary vascular markings
RA = right atrium
RV = right ventricle
PA = pulmonary artery

RESULTS

I. *Preoperative Physiological Studies.*—The presence of an atrial septal defect was confirmed by right-heart catheterization in all but one case. In this patient (R.B.), the defect was discovered during the course of a mitral commissurotomy. No preoperative physiologic data were obtained in this case, the sole example of Lutembacher's syndrome in this series. The catheter was passed through the defect in two patients (G.S. and M.S.). In one individual (M.S.), anomalous pulmonary venous drainage into the right atrium was diagnosed preoperatively. In the other (T.S.), the anomaly was found at surgery. This complicating lesion was ruled out at the time of surgery in all other patients.

The most constant finding in the group was increased pulmonary blood flow. This ranged between 6.2 and 31 L./min.; that is, 1.4 to 8.7 times the systemic blood flow. The latter was considered within normal limits at rest in all but three cases, (W.B., H.W., and G.C.), in whom it was low.

The over-all intracardiac shunt was left to right in all cases, the total left-to-right shunt ranging between 3.0 to 27.6 L./min. The brachial arterial saturation was below normal in three patients (T.S., J.C., and H.W.), indicating, in addition, a right-to-left shunt. In only one case (J.C.) did this exceed one liter. The magnitude of the right-to-left shunt was insufficient to produce cyanosis in any individual.

The pulmonary arterial pressure was within normal limits in six patients and elevated in seven. In one patient (G.S.), the pulmonary artery could not be entered by the catheter preoperatively. However, she had an elevated right ventricular systolic pressure. In the second (R.B.), the case of Lutembacher's syndrome, no physiologic data were obtained preoperatively.

Pulmonary resistance was elevated in three cases. It was normal or low in the remaining eleven patients, in whom it was calculable. Right ventricular work was calculated in twelve cases and found increased in seven.

II. *Postoperative Physiological Studies.*—Postoperative catheterization revealed elimination of the left-to-right shunt in eleven cases. There was no evidence of a left-to-right shunt in the twelfth case, R.B., in whom no preoperative physiologic data were obtained.

In these individuals there was an appreciable drop in the oxygen content of the pulmonary arterial blood. In one patient (J.S.), a single highly oxygenated sample was obtained in the right atrium. Since the oxygen content of blood samples obtained central to this point, i.e., from the right ventricle and pulmonary artery, showed no significant increase over blood samples obtained from other sites in the right atrium and superior and inferior vena cava, any left-to-right shunt at this level could not be considered physiologically significant. Furthermore, there was an appreciable fall in oxygen content of pulmonary arterial blood, not entirely accounted for by a slight fall in the hemoglobin postoperatively. Also in favor of elimination of the left-to-right shunt was the marked increase in the brachial artery-pulmonary artery oxygen difference postoperatively. There was a fall in the pulmonary arterial pressure, as well, following surgery in this case.

In one case (J.C.), there was little change in the shunts following surgery. In another (C.S.), the calculated left-to-right shunt was less postoperatively. The decrease was more apparent than real. The preoperative systemic flow was calculated employing superior vena cava oxygen content alone, while postoperatively both superior and inferior vena cava contents were considered. This would tend to reduce the systemic blood flow preoperatively and increase the left-to-right shunt. Since the oxygen content of the pulmonary arterial blood was unchanged, it suggests that the left-to-right shunt is still present.

Concurrently with the elimination of the left-to-right shunt, there was a reduction in the pulmonary blood flow in these subjects. In two patients (A.C. and H.W.), the PBF remained elevated; both exhibited anxiety during the postoperative catheterization. In both, the oxygen consumption during the latter procedure was significantly higher than preoperatively. These factors may account for the elevated flows. There was no evidence for a shunt in these two cases.

The pulmonary arterial pressure fell postoperatively in several patients (Table II). The most significant change occurred in patient P.F. It is to be noted that the fall in the pulmonary arterial pressure occurred during systole with little change in the diastolic pressure. Both pressures, however, remained elevated following surgery. In the other individuals a slightly elevated pulmonary arterial pressure fell to within normal limits. In G.S., in whom no pulmonary arterial pressure was obtained preoperatively, there was a significant drop in the right ventricular systolic pressure following surgery.

The work of the right ventricle decreased with a fall in the input load and pulmonary arterial pressures. In all but three patients (C.F., A.C., and H.W.), the right ventricular work fell to within the normal range. In two of these (A.C. and H.W.), the cardiac output was elevated during the second catheterization due to a high oxygen consumption. In the third (C.F.), the pulmonary arterial pressure remained elevated, accounting for the increased right ventricular work.

CLINICAL CHANGES FOLLOWING ATRIO-SEPTO-PEXY

Decreased exercise tolerance and exertional dyspnea were the most common symptoms prior to surgery (Table I). Several patients had palpitations, due to paroxysmal tachycardia or frequent premature systoles. Others complained of chest pain. There was improvement or disappearance of these symptoms in all patients but one (J.C.).

Relief of dyspnea might be attributed to two factors: (1) reduction in pulmonic blood flow, and (2) more adequate cardiac output during exercise.

It has been shown experimentally that pulmonary congestion causes a diminished distensibility of the lungs.[11] This would suggest that the dyspnea in atrial septal defect is due to the "rigidity" imposed upon the lung secondary to an increased rate of flow through the pulmonary bed. This symptom disappeared or was markedly decreased following closure of the defect with elimination of the left-to-right shunt.

TABLE II. PHYSIOLOGIC DATA BEFORE

CASE	RA (MEAN)	RV S/D	PA S/D (MEAN)	PVC (MEAN)	PULM. RESIST. (DYNES/SEC./CM^{-5})	RV WORK (KG. M./MIN.)	BA S/D	SVC	IVC
C.F. Preop.	4	67–70 / 2–4	70–74 / (34–40) / 30–32	—	369	2.05	110 / 64	13.6	17.1
Postop., 12 mo.	6	58–68 / 5	57–65 / (39) / 20–30	8	547	1.65	140 / 76	—	15.6
J.S. Preop.	4	31 / 4	31 / (21) / 15	—	54	7.64	—	13.9	13.7
Postop., 6 wk.	—	18–20 / −2–0	18–20 / (12) / 4–6	—	309	0.44	—	9.8	—
M.S. Preop.	4	20–22 / 2	20–22 / (10) / 2–4	—	105	0.68	—	—	12.8
Postop., 3 wk.	0	18–20 / 0	20 / (10) / 4	—	186	0.38	—	9.5	—
R.B. Preop.	—	—	—	—	—	—	—	—	—
Postop., 3 mo.	0	28–35 / −2–2	25–34 / (10–14) / 4–12	12	209	0.61	—	8.4	8.7
J.C. Preop.	−2	90–100 / −4–0	90–105 / (55–70) / 38–40	—		3.42	138 / 75	14.4	14.0
Postop., 5 mo.	6	80–85 / 7	84–88 / (56) / 40–42	—		3.16	84 / 52	11.8	
T.S. Preop.	5	41–51 / (25–30) / 2–5	38–41 / 17		—	—		11.5	12.6
Postop., 6 wk.	2	10–13 / −2–0	10–15 / (10) / 6–9	9	—	—	105 / 59		8.6
P.F. Preop.	5	90 / 10	90 / (65) / 40	—	300	—		12.2	—
Postop., 17 days	5	45–50 / 0	45–50 / (40) / 30–35	—	532	—		10.0	11.4
M.K. Preop.	5	22–27 / 2–5	22–25 / (11–15) / 5–7	—	60	1.96	102 / 60	8.3	10.1
Postop., 23 days	5	17–20 / 0	18–20 / (15) / 10	10	207	0.75	116 / 56	6.4	7.6

AND AFTER ATRIO-SEPTO-PEXY

OXYGEN CONTENT (VOL. %)										O_2 CONS.	FLOWS			SHUNTS		
RA			RV			PA	PV* LA**	BA			SBF	PBF	EPBF	TOTAL L-R	TOTAL R-L	OVER-ALL L-R
HIGH	MID	LOW	HIGH	MID	LOW			CONT.	SAT.							
16.4	16.2	16.6	—	17.9	18.1	17.9	—	21.4	94.3	268	4.5	7.8	4.5	3.3	0	3.3
—	—	14.5		14.6	14.6	14.5	—	20.1	93.1	321	5.7	5.7	5.7	0	0	0
18.0	—	17.8	—	17.3	17.6	17.6	—	18.1	97	156	3.6	31.2	3.6	27.6	0	27.6
9.8	14.8	9.8	10.3	10.3	—	10.8		15.4	88	140	3.1	3.1	3.1	0	0	0
15.3	14.2	15.2	15.5	15.1	—	15.0	15.5** 17.0*	16.8	93.3	156	3.9	7.8	3.9	3.9	0	3.9
9.0	9.7	9.3	9.8	—	—	9.7	—	13.4	90.6	160	4.3	4.3	4.3	0	0	0
—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
8.0	9.2	9.3	9.2	—	9.9	9.6		12.8	91.5	147	4.6	4.6	4.6	0	0	0
16.9	16.3	16.9	16.9	15.1	17.4	16.6	17.2**	20.2	87.5	322	5.4	6.2	4.2	2.2	1.0	1.1
14.4	14.4	14.4	13.9	14.1	—	14.0		17.0	88.6	286	5.5	6.8	4.5	2.3	1.0	1.3
13.1	14.1	13.8	13.6	13.4	—	13.5		14.0	91	—	—	—	—	—	—	—
—	9.6	9.6	—	9.6	9.5	9.6		13.5	85.5	—	—	—	—	—	—	—
13.4	15.9	15.7	—	15.7	15.9	16.0		16.9	94	190	4.0	17.3	4.1	13.2	0	13.2
12.0	12.0	—	11.9	11.5	11.7	11.5		14.5	82.5(a)	177	5.9	5.9	5.9	0	0	0
11.3	12.7	12.5	13.2	13.0	—	13.0		14.3	98	227	4.5	17.5	4.5	13.0	0	13.0
6.9	6.4	7.3	6.6	—	7.7	7.3		10.6	84.2	192	5.8	5.8	5.8	0	0	0

TABLE II. PHYSIOLOGIC DATA BEFORE

CASE	RA (MEAN)	RV S/D	PA S/D (MEAN)	PVC (MEAN)	PULM. RESIST. (DYNES/SEC./CM^{-5})	RV WORK (KG. M./MIN.)	BA S/D	SVC	IVC
J.B. Preop.	−2	10 / −4-2	6-10 / (3) / −2-0	—	22	0.29	98 / 60	12.3	—
Postop., 6 mo.	1	20 / 0	20 / (16) / 10	—	410	0.43	130 / 80	13.1	15.2
A.C. Preop.	1	30-38 / 0	30-40 / (18) / 10-14	5	77	2.74	104 / 60	10.5	14.2
Postop., 4 mo.	8	30-35 / 3	30-35 / (22) / 10-15	—	284	1.11	140 / 70	11.8	12.5
C.S. Preop.	2	24 / 7	23 / (14) / 10	5	160	0.83	135 / 90	15.6	—
Postop., 7 mo.	2	22 / 2	20 / (10) / 8	7	129	0.53	140 / 78	15.3	18.3
G.S. Preop.	0	46 / 0	—	—	—	—	144 / 44	—	14.3
Postop., 3 mo.	0	20 / 2	18 / (9) / 6		151	0.41	136 / 60	12.4	13.7
N.H. Preop.	1	20 / 0	26 / (10) / 6	—	86	0.65	120 / 80	13.2	—
Postop., 12 mo.	0	20 / 2	20 / (10) / 8	—	140	0.40	120 / 76	14.1	—
H.W. Preop.	0	45 / 0	44 / (29) / 11	4	250	2.36	110 / 70	11.9	13.9
Postop., 3 mo.	0	28 / 0	28 / (18) / 14	—	206	1.10	132 / 70	11.9	13.1
G.C. Preop.	0	28 / 0-2	30 / (23) / 12	—	156	2.23	100 / 60	11.1	10.6
Postop., 14 mo.	0	20 / 0	20 / (10) / 6	0	242	0.27	120 / 60	—	12.1

(a) BA Sat. 3 mo. postop. 95 per cent.

AND AFTER ATRIO-SEPTO-PEXY (CONT'D)

OXYGEN CONTENT (VOL. %)										O_2 CONS.	FLOWS			SHUNTS		
RA			RV			PA	PV* LA**	BA								
HIGH	MID	LOW	HIGH	MID	LOW			CONT.	SAT.		SBF	PBF	EPBF	TOTAL L-R	TOTAL R-L	OVER-ALL L-R
13.4	15.9	15.7		15.7	15.9	15.9		16.9	92	110	2.4	11.0	2.4	8.6	0	8.6
13.2	13.5	13.8		13.5	—	12.8		17.4	93.5	142	3.1	3.1	3.1	0	0	0
13.5	15.9	15.5	16.0	15.9	—	16.0		17.3	94.5	243	5.0	18.7	5.0	13.7	0	13.7
11.5	12.0	11.8	12.2	—	—	11.6		16.9	95.8	328	6.2	6.2	6.2	0	0	0
17.5	18.2	16.8	—	18.6	19.0	18.5		20.8	94	160	3.1	7.0	3.1	3.9	0	3.9
17.3	17.7	17.6		17.8	17.7	18.2		21.2	93.4	187	4.3	6.2	4.3	1.9	0	1.9
16.2	16.7	15.9	—	—	—		17.9**	18.7	91.7	—	—	—	—	—	—	—
11.4	14.3	—	12.9	13.2	—	13.4		16.8	94.9	162	4.8	4.8	4.8	0	0	0
19.2	18.0	17.6	18.7	18.8	17.7	18.6		20.8	97.2	204	2.7	9.3	2.7	6.6	0	6.6
12.8	15.3	14.9	14.4	14.4	14.6	15.9		20.7	94.5	275	5.7	5.7	5.7	0	0	0
14.9	18.2	17.1	17.8	18.0		18.1	19.4*	18.3	87.6	121	2.2	9.3	1.9	7.4	0.3	7.1
10.1	13.3	12.8	—	12.3	12.9	12.4		17.7	92.7	370	7.0	7.0	7.0	0	0	0
13.5	16.1	17.4	16.9	17.4	—	17.3		18.9	93.1	165	2.1	11.8	2.1	9.7	0	9.7
—	—	11.8	12.1	12.5	—	12.5		16.4	97.8	127	3.3	3.3	3.3	0	0	0

Although patients with atrial septal defect may show a rise in the systemic flow during exercise, the rise is probably insufficient to meet the demands of the tissues. A compensatory increase in ventilatory effort results. Relief of dyspnea following closure of the defect would suggest that the cardiac (left ventricular) output is now more adequate. In this regard it is of interest to note that the systemic flow rose to within normal limits in three individuals in whom it was low prior to surgery.

The nature of the chest pain is unknown. If it is cardiac in origin, it may be due to relative coronary insufficiency; i.e., coronary flow, though normal, is inadequate to meet the demands of the over-burdened heart. With reduction in the work load of the heart following surgery, the need for coronary flow is reduced.

A constant finding on physical examination in this group was a systolic murmur in the pulmonic area or along the left sternal border. Findings at surgery and following atrio-septo-pexy suggest that this murmur is due to an increased rate of flow through a normal pulmonic valve into a dilated artery. This is suggested by the presence of a thrill over the pulmonary artery prior to closure of the defect. This thrill is markedly reduced or disappears following closure of the defect. Postoperatively the systolic murmur disappeared in all but four individuals. The persistence of the murmur in some patients may be due to eddy currents within the still dilated artery beyond the rigid ring of the pulmonic valve during ventricular systole.

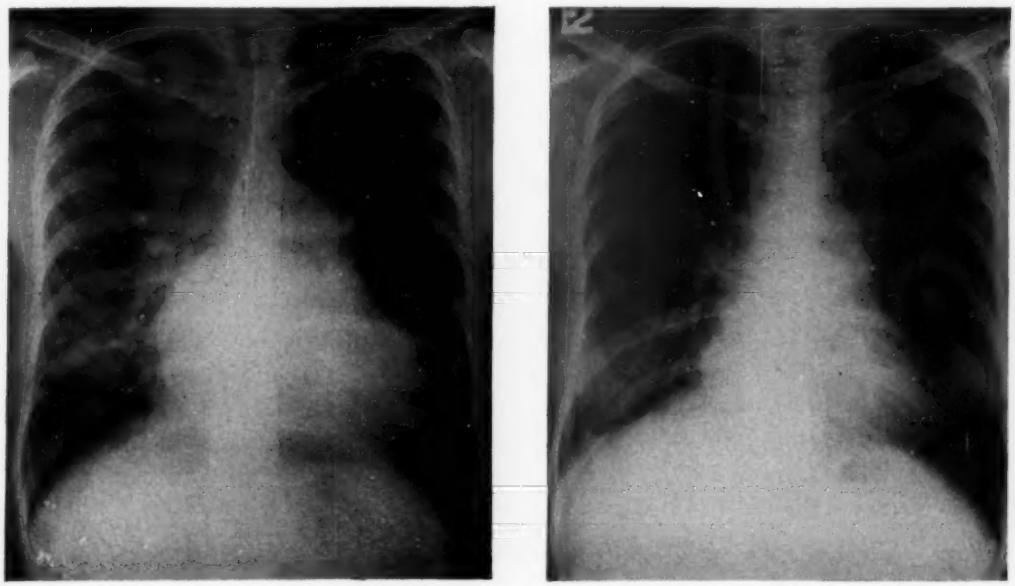
The second pulmonic sound was increased in intensity in the majority of patients. The mechanism is not clear. Although found in all patients with pulmonary hypertension, the observation was made in individuals with normal pulmonary arterial pressures. Although postoperatively it became normal in some individuals, it remained accentuated in many despite reduction in pulmonic blood flow and pressures.

Several individuals had diastolic murmurs. The early diastolic murmur along the left sternal border, probably due to pulmonary insufficiency, was observed preoperatively in one patient (H.W.). The murmur disappeared following surgery in this case. A mid-diastolic murmur suggesting the presence of mitral stenosis was observed in three patients. Only one, R.B., had an associated mitral stenosis. In our experience, the combination of atrial septal defect and mitral stenosis has been relatively rare. Patients in whom the diagnosis of Lutembacher's syndrome is entertained are usually shown to have either atrial septal defect alone or mitral stenosis with pulmonary vascular changes and a dilated pulmonary artery. Recently we have observed a patient with the auscultatory findings of mitral stenosis who roentgenographically showed a large pulmonary artery with only minimal left atrial enlargement. At surgery this patient was found to have mitral stenosis and anomalous pulmonary venous drainage of the left upper lobe of the lung into the left innominate vein.[12] This combination, though rare, would simulate the dynamics of Lutembacher's syndrome.

The mid-diastolic murmur in an uncomplicated atrial septal defect may be due to: (1) increased rate of blood flow through a normal tricuspid valve, or

(2) blood flow across the defect per se. The disappearance of this murmur following closure of the defect would suggest either of these possibilities.

The electrocardiogram was abnormal in thirteen cases. A normal sinus rhythm was present in all preoperatively, and right-heart strain pattern was observed in nine cases. Right bundle branch system block was found in four patients; incomplete in two and complete in two. In two individuals the tracing was within normal limits. Changes in rhythm are frequently observed during and immediately following atrio-septo-pexy. These consisted chiefly of atrial arrhythmias such as premature systoles, tachycardia, flutter, and fibrillation.



A. *B.*

Fig. 1. Anteroposterior roentgenograms before (*A*) and 3 months after (*B*) atrio-septo-pexy in patient H. W.

In many instances these reverted spontaneously to normal. Some patients reverted to a sinus rhythm shortly after receiving a digitalis preparation. In one patient (G.S.), atrial fibrillation persisted up to three months, with conversion to normal sinus rhythm with institution of quinidine therapy. In all patients but one (A.C.), there was eventual reversion to a normal sinus mechanism. This patient developed complete atrioventricular block which was still present seven months after surgery. It is interesting to note that in this patient the atrial defect was closed and the shunt eliminated with marked improvement in the clinical picture. Injury to the atrioventricular node probably accounts for the persistence of the arrhythmia.

The most striking change on roentgenographic examination was a decrease in the pulmonary vascular markings. The cardiac silhouette showed some decrease in size in many patients (Fig. 1). One patient (J.C.), in whom there was no significant change in the cardiodynamics after surgery, was seen to have an increase in cardiac mass. The changes in the vascular markings and heart size

are probably an expression of the reduction in pulmonary blood flow secondary to elimination of the left-to-right shunt.

DISCUSSION

The hemodynamic data before and after surgery indicate that atrio-septopexy can effectively relieve the burden imposed upon the circulation by atrial septal defect. This lesion, in its uncomplicated form, physiologically represents an intracardiac arteriovenous shunt. That is, a defect in the atrial septum allows blood to flow from the left atrium to the right atrium with a subsequent increase in the input load into the right ventricle. Consequently, there is an increase in work of this chamber as well as an increase in the quantity of blood flowing through the pulmonary bed.

Although several mechanisms have been invoked to explain the left-to-right shunt in atrial septal defects,[13-15] it appears that the most important factors concern themselves with the pressure-volume relationships of the cardiac chambers. It has been shown experimentally that the left atrium is less distensible than the right atrium.[16] This may be related to the relative thickness of the two atria, the left being thicker than the right. The reservoir on the right side (superior and inferior venae cavae) is probably larger than that on the left (pulmonary veins). In the presence of an interatrial communication with blood flowing into both atria, the pressure will build up more rapidly in the less distensible left atrium with a pressure gradient developing to favor flow from left to right. In addition, it is suggested that the direction of flow thus described is also related to the relative resistance to filling of the two ventricles.[17] The thin-walled right ventricle is more distensible than the thicker left ventricle; hence, the right ventricle is capable of readily accepting larger quantities of blood than the left ventricle. These differences in the pressure-volume relationships of the two ventricles are undoubtedly a reflection of the relative resistance of the two major circuits: the low resistant pulmonary versus the high resistant systemic circulation. This is the picture in atrial septal defect uncomplicated by pulmonary vascular changes.

The circulatory dynamics become altered in the presence of pulmonary vascular changes. Although the pulmonary arterial pressure may remain within normal limits in spite of marked increases in flow due to the vast capacity of the pulmonary bed, pulmonary hypertension is frequently observed.

In the majority of instances, particularly when the elevation in the pulmonary arterial pressure is marked, pulmonary vascular changes resulting in an increased resistance to flow are a major factor. That abnormally increased flows into a normal pulmonary bed may result in mild degrees of pulmonary hypertension is suggested in some patients (T.S. and G.S.). Pulmonary hypertension may result from large flows into a pulmonary bed restricted in part by vascular changes, e.g., patient P.F. In this case, there was a significant drop in the pulmonary arterial pressure seventeen days postoperatively. The pressure did not return to normal despite marked reduction in blood flow, suggesting the presence of residual vascular change resulting in increased pulmonary resistance.

Pulmonary vascular changes, the anatomic counterpart of the increased resistance to blood flowing through the pulmonary bed observed physiologically, have been described in atrial septal defect.[18] The developmental factors involved in these changes remain obscure. Obvious factors would appear to be (1) increased pulmonary blood flow, and (2) highly oxygenated blood flowing through the pulmonary vascular bed.

It does not appear from our studies[19] that the magnitude and duration of the left-to-right shunt are the determining factors. Pulmonary hypertension and increased pulmonary vascular resistance may be observed at early ages, while normal pressures in the presence of a large flow in the pulmonary circuit may be present in the older age group.

Characteristically, in atrial defect, the blood traversing the pulmonary bed has an abnormally high oxygen content. It is suggested that this is a factor in initiating the pulmonary vascular changes which are perpetuated by structural changes in the smaller pulmonary vessels consisting of medial hypertrophy and intimal fibrosis. A superimposed functional narrowing cannot be eliminated. The development of pulmonary changes appears to be a response on the part of the individual in an attempt to reduce the left-to-right shunt thus tending to equalize the flows in the two major circuits: the pulmonary and the systemic.

The resistance to flow of blood through the pulmonary bed is increased, and the pulmonary artery pressure rises. The latter may cause aggravation of the anatomic changes described previously with further increase in the resistance to blood flow. It is apparent that in some individuals this resistance may progress to a point where blood leaving the right atrium finds it easier to traverse the defect into the left atrium than to pass through the pulmonary circuit.

The mechanism for the alteration in the circulatory dynamics in the presence of pulmonary vascular changes is as follows: these changes, by virtue of increasing resistance to flow through the pulmonary circuit, result in right ventricular hypertension and increased work of this chamber. The right ventricle thus hypertrophies and its pressure-volume relationships change, becoming less distensible than formerly. It now offers more resistance to inflow of blood from the right atrium. Consequently, there is an increase in the residual blood in the right atrium at the end of rapid filling of the ventricle during diastole. According to Starling's law, this results in a more forceful contraction of the right atrium. This eventually leads to hypertrophy and similarly a change in the pressure-volume relationships of the right atrium. This is suggested by the more sweeping pressure changes occurring in this chamber during the cardiac cycle in these patients.[19] Hence, the major factor responsible for the direction of flow of blood (left to right) through uncomplicated atrial defects, i.e., the relatively less distensibility of the right atrium, is altered. Accordingly, the left-to-right shunt is reduced. Progression in the hypertrophy of the right-heart chambers may result in reversal of the shunt with the appearance of peripheral arterial hypoxemia and cyanosis. Thus it appears that cyanosis in atrial septal defect, uncomplicated by other cardiac malformations, may occur in the absence of right-heart failure. In our experience[19] chronic cyanosis in atrial septal defect uncomplicated by other lesions has been associated with severe pulmonary hypertension with markedly increased pulmonary vascular resistance.

SUMMARY

1. The physiological and clinical changes following closure of atrial septal defect in fifteen patients by the atrio-septo-pexy technique are presented.

2. The hemodynamic studies reveal complete elimination of the left-to-right shunt in twelve cases. In two patients the shunt was decreased, and there was no change observed in one.

3. The significance of the clinical changes following surgery is discussed.

SUMMARIO IN INTERLINGUA

Es discutite le alterationes physiologic e clinic sequente le clausura de defectos atrioseptal executate in 15 patientes secundo le technica atrioseptopexic describite in 1952 per Bailey e alteros.

Studios hemodynamic revelava le complete elimination del derivation ab le sinistra verso le dextera in 12 del 15 casos. In duo patientes le derivation esseva reducite. In un patiente nulle alteration esseva observate. Le elimination del derivation esseva accompaniate per un reduction in le fluxo de sanguine pulmonar. Le pression pulmonoarterial, elevate ante le operation, se reduceva post le intervention chirurgic in plure patientes. In omne patientes, con un exception, melioration o alleviamento del symptomas esseva observate.

Nos discute le signification del alterationes clinic observate post le operation atrioseptopexic.

The authors wish to express their appreciation to Mr. George Reber and Misses Betty Underwood, Ruth Freeman, and Evelyn De Simone for their technical assistance, and to the other members of the cardiac catheterization team.

REFERENCES

1. Brannon, E. S., Weens, H. S., and Warren, J. V.: Atrial Septal Defect: Study of Hemodynamics of the Technique of Right Heart Catheterization, Am. J. M. Sc. **210**:480, 1945.
2. Taylor, B. E., Gerace, J. E., Pollack, A. A., Burchell, H. B., and Wood, E. H.: Interatrial Mixing of Blood and Pulmonary Circulatory Dynamics in Atrial Septal Defects, Proc. Staff Meet., Mayo Clin. **23**:500, 1948.
3. Bailey, C. P., Downing, D. F., Geckeler, G. D., Likoff, W., Goldberg, H., Scott, J. C., Janton, O., and Redondo-Ramirez, H. P.: Congenital Interatrial Communications; Clinical and Surgical Considerations With a Description of a New Surgical Technique: Atrio-septo-pexy, Ann. Int. Med. **36**:888, 1952.
4. Bailey, C. P., Bolton, H. E., Jamison, W. L., and Neptune, W. B.: Atrio-septo-pexy for Interatrial Septal Defects, J. Thoracic Surg. **26**:184, 1953.
5. Neptune, W. B., Bailey, C. P., and Goldberg, H.: The Surgical Correction of Atrial Septal Defects Associated With Transposition of the Pulmonary Veins, J. Thoracic Surg. **25**:623, 1953.
6. Miller, G., Goldberg, H., Elisberg, E., Snider, G., Toor, M., and Katz, L. N.: Cardiopulmonary Studies in Patients with Mitral Stenosis. I. Circulatory Dynamics, J. Lab. & Clin. Med. **40**:390, 1952.
7. Van Slyke, D. D., and Neill, J. M.: Determination of Gases in Blood and Other Solutions by Vacuum Extraction and Manometric Measurement, J. Biol. Chem. **61**:523, 1923.
8. Holling, H. E., and Zak, G. A.: Cardiac Catheterization in the Diagnosis of Congenital Heart Disease, Brit. Heart J. **12**:153, 1950.
9. Handleman, J. C., Bing, R. J., Campbell, J., and Griswald, E.: Physiological Studies in Congenital Heart Disease—The Circulation in Patients With Isolated Septal Defects, Bull. Johns Hopkins Hosp. **82**:615, 1948.
10. Gorlin, R., Haynes, F. W., Goodale, W. T., Sawyer, C. G., Dow, J. W., and Dexter, L.: Studies of the Circulatory Dynamics in Mitral Stenosis, Am. Heart J. **41**:30, 1951.

11. Mack, I., Grossman, M., and Katz, L. N.: The Effect of Pulmonary Vascular Congestion on the Distensibility of the Lungs, Am. J. Physiol. **150**:654, 1947.
12. Nichols, H., Waldow, A., and Goldberg, H.: Mitral Stenosis Associated With Anomalous Pulmonary Venous Drainage: Report of a Case With Surgical Correction of Both Lesions, (To be published).
13. Uhley, M. H.: Lutembacher's Syndrome and a New Concept of the Dynamics of Interatrial Septal Defect, AM. HEART J. **24**:315, 1942.
14. Cournand, A., Motley, H. L., Himmelstein, A., Dresdale, D., and Baldwin, J.: Recording of Blood Pressure From the Left Auricle and Pulmonary Veins in Human Subjects With Interauricular Septal Defect, Am. J. Physiol. **150**:267, 1947.
15. Hull, E.: The Cause and Effects of Flow Through Defects of the Atrial Septum, AM. HEART J. **38**:350, 1949.
16. Little, R. C., Opdyke, D. F., and Hawley, J. C.: Dynamics of Experimental Atrial Septal Defects, Am. J. Physiol. **158**:241, 1949.
17. Barger, J. D., Edwards, J. E., Parker, R. L., and Dry, T. J.: Atrial Septal Defect: Presentation of a Case With Obstructed Pulmonary Vascular Lesions Caused by Metastatic Carcinoma, Proc. Staff Meet., Mayo Clin. **23**:182, 1948.
18. Welch, K. J., and Kinney, T. D.: The Effect of Patent Ductus Arteriosus and Interauricular and Interventricular Septal Defects on the Development of Pulmonary Vascular Lesions, Am. J. Path. **24**:729, 1948.
19. Unpublished observations.

THE ACCURACY OF THE VECTORIAL INTERPRETATION OF ELECTROCARDIOGRAPHIC TRACINGS

J. Araújo Moreira, M.D., Ph.D.

Lisbon, Portugal

ONE of the most controversial (and fundamental) problems of electrocardiography is that of determining the limits within which is legitimate a vectorial interpretation of the tracings. This would be theoretically justified if the heart was placed in an indefinite homogeneous space and the electrodes at sufficiently great distances or in the center of a sphere with a big radius and the electrodes at the surface. The field (supposed stationary) at each instant would be approximately equivalent to the field of an electric dipole, and the extremities of the successive instantaneous dipoles would describe in a cardiac cycle a curve: the "real" vectorcardiogram. This vectorcardiogram, as a curve independent of the positions of the electrodes relative to the heart, would be very useful if it could be known.

The construction of vectors, in search of such invariants, initiated by Einthoven,[1] has been effectively one of the most important tasks of the electrocardiographers. Restricted at first to isolated vectors, it was later possible to calculate and record curves that were believed to represent approximately the real vectorcardiogram.[2-5] But generally the methods implicated the admission that the human body was an indefinite homogeneous space and none or only gross corrections were made for the different distances of the electrodes to the heart and the variable internal angle of the leads.

As the human body is undoubtedly limited and heterogeneous, it is difficult to judge the accuracy with which the curves obtained represent effectively the "real vectorcardiogram." The technique of Bürger and van Milaan[6] has been proposed with full appreciation of this problem, but unfortunately the solution is not satisfactory, particularly on account of the implicated similarity of the human body and a certain model.

In view of the fact that the electric cardiac field must not only be complex, but also very probably, at the surface of the body, of a structure different from subject to subject (particularly in the pathological cases, which are clinically the most important) it seems to us that the only satisfactory method is the one which enables us to determine in each case the degree of validity of the vectorial interpretation and accuracy of the vectorcardiographic techniques available.

From the Department of Cardiology, Instituto Portugues de Oncologia, Lisbon, Portugal.
Received for publication Aug. 9, 1954.

The present study was undertaken in an effort to obtain such a method.[7-9] It consists essentially in the unrestricted admission of the hypothesis necessary for the representation of the cardiac electric field, at each instant, by a vector, and the comparison of the real relations of sets of curves obtained in each subject with those so theoretically predicted.

METHODS AND EXAMPLES

If the hypothesis of the dipole centered in a sphere is admitted, it can be demonstrated (Appendix I) that the difference of potential between a point P (for instance on the thorax) and points P_i equidistant from P is a linear function of the cosine of the angles α_i between the plane defined by P and the dipole and that determined by the directions of P and P_i (Fig. 1). We may write

$$V_{P_i} - V_P = S + T \cos \alpha_i.$$

The accuracy with which this relation is verified may be considered a measure of the validity of the hypothesis and consequently of the vectorial interpretation of the tracings.

As S is proportional to the potential V_P of the unipolar at P, the potential of a conductor ring with center at P and consequently the difference of potential between a point P and the ring are also proportional to the potential V_P. For the registering of these last differences, we use the electrode represented in Fig. 2 (distance D between the central electrode and the concentric ring = 5 cm.). In the regions where the field is equivalent to that of a dipole the pattern of the bipolar so obtained (we call it "equivalent bipolar, that is, B_E") must be the same as that of the Wilsonian unipolar U_W obtained at the point at which the central electrode is placed.

The ratio of the amplitudes of the equivalent bipolar and the unipolar is a function of the distance *d* at which is the dipole; in fact,

$$\frac{\text{amplitude of equivalent bipolar}}{\text{amplitude of unipolar}} = 1 - \cos \frac{D}{d}.$$

With the nomogram of Fig. 3 it is possible to obtain directly the distance *d* from the amplitudes of the bipolar and the unipolar (for D = 5 cm.).

Practically, in our investigations, we chose a region on the thorax and a point P and points P_i within this (the points P_i at 5 cm. from P and at angular distances of 60°, the successive points 1, 2 . . . 6 being taken in a clockwise direction). In all our cases, the point 1 corresponds to the value 0 of the angle γ (Appendix I). This point 1 is always in a horizontal line passing at P and at the right of this point.

We used a Sanborn stethocardiette. The tracings $V_{Pi} - V_P$ were obtained with the positive electrode fixed at P_i and the negative at P. For the equivalent bipolar the polarity was such that the central point P was the positive pole. The standardization employed is shown with the records.

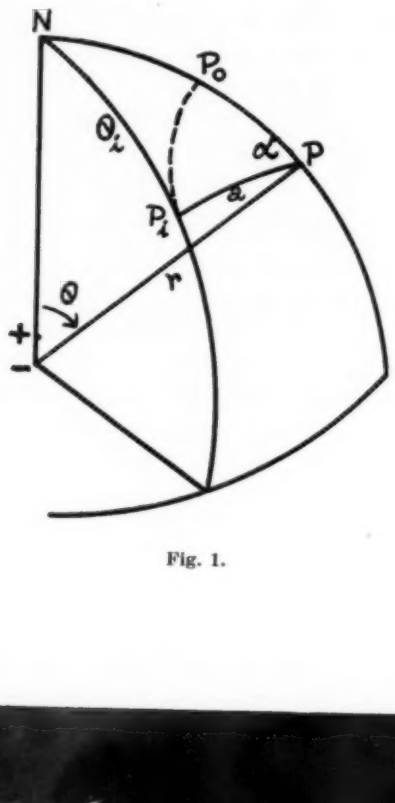


Fig. 1.

Fig. 2.

Fig. 3.—Nomogram to find directly d and the angle a. The value of B_E is plotted on the right scale and that of U_W on the left. The straight line, drawn from these two points, determines a point in the third scale where we can read the corresponding distance of the dipole (and the angle d).

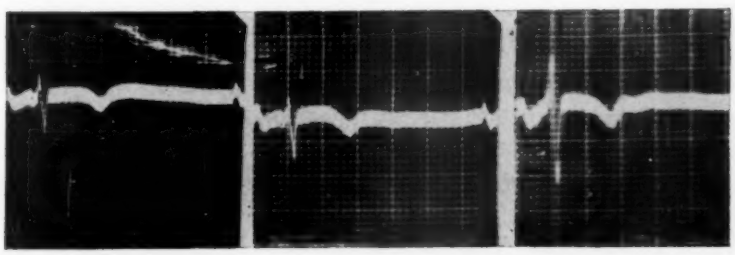


Fig. 4.

A. *The Similarity of the Unipolars and the Equivalent Bipolars.*—In Fig. 4 we have a first example of the aspect of the equivalent bipolar, confronted with the corresponding Wilsonian unipolar. The first and second tracings of Fig. 4 are B_E, the last a U_W. The first one was obtained with the electrode of Fig. 2, the second at the same place but with ordinary electrodes for precordials, one at the point P and the other at the conductor ring of jelly left by the ring electrode.

B. *The Calculation of the Vectors.*—If B_E is similar to U_W, it is probable that this lead is vectorial, and we may try to construct the vectors. In Fig. 5, *A* to *D*, it is shown how in a case, the mean vector was determined from leads made in the region of the point C_5 (Fig. 5*D*). P_1, P_2, . . . P_6 (Fig. 5*A*) represent the tracings of the differences of potential between the points 1, 2 . . . 6 and the point C_5 (Fig. 5*D*); the points 1, 2 . . . 6 are 5 cm. from C_5, *1* on a horizontal line and to the right of C_5 as already mentioned. The areas of the accidents QRS in each tracing were plotted against the angles $\gamma = 0°$, $\gamma = 60°$ . . . $\gamma = 300°$ corresponding to each P_i in a system of orthogonal axis (Fig. 5,*C*).

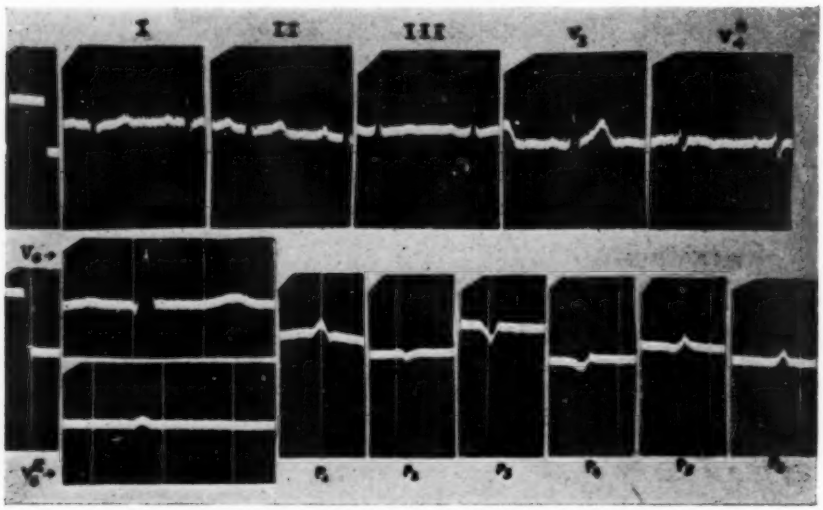


Fig. 5*A*.

In this case, the points found trace approximately a sinusoid. (If they do not trace such a sinusoid as in the cases of Fig. 6, *A* and *B*, the calculations that follow are not legitimate.)

The position of the symmetric axis (parallel to the axis where we plot the angles) is determined by the area of the B_E which is equal to $-S$. To determine the best sinusoid, we use a family of sinusoidal curves (identical to those of Fig. 5,*B*) traced on transparent paper. When the best sinusoid is found, we have the value of the angle γ corresponding to $\alpha = 0$ at the maximum S + T. T is also automatically determined. Of course, all the tracings must be reduced to the same standardization and velocity of the paper.

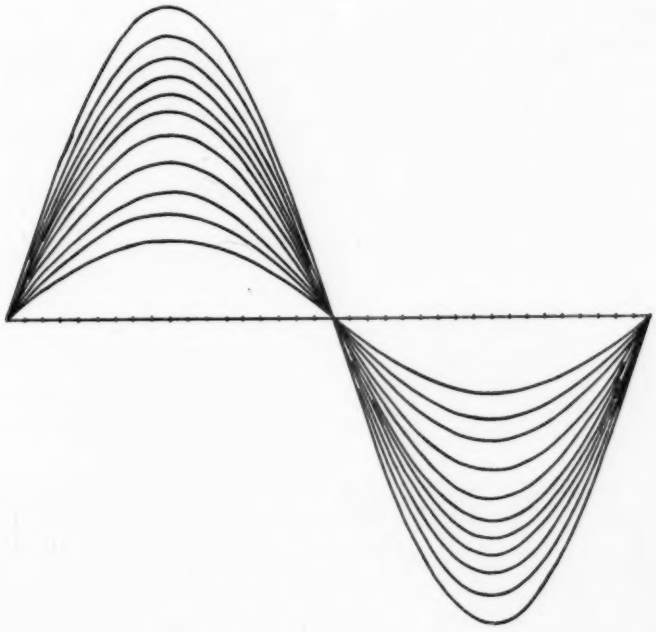
In the case of Fig. 5, *A* to *D*, the tracings of Fig. 5, *A* were amplified ten times and the areas determined in cm^2.

We have calculated

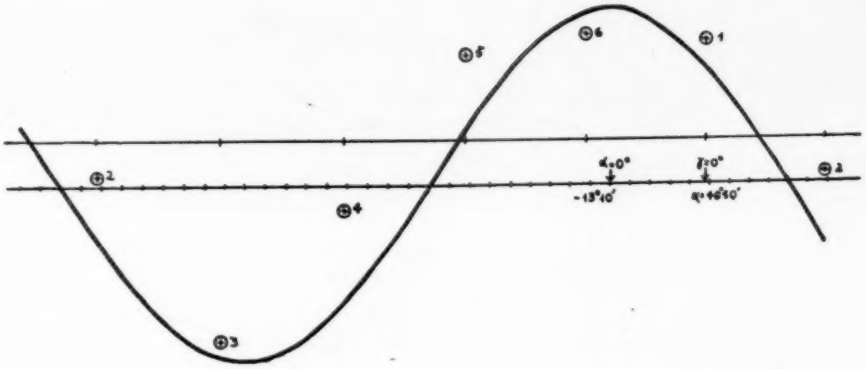
$$\frac{B_E}{U_W} = 1 - \cos a = 0.083; \; B_E = -S = 1.3.$$

The sinusoidal curve chosen is that of Fig. 5, *C* which gives T = 5 and $\alpha = 46°50'$ for $\gamma = 0$. From S, T, and a we calculated T_g. $\theta = 0.8$; $\theta \cong 38°$, $K \cong 20°$.

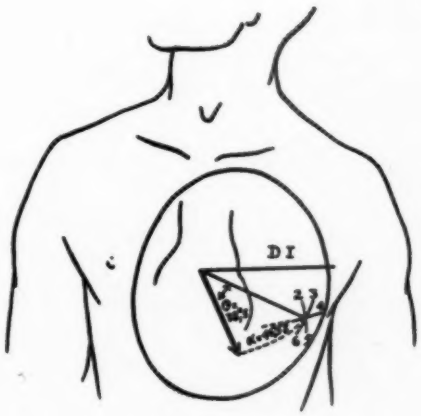
The vector determined by these values is represented in Fig. 5, *D*.



B.



C.



D.

Fig. 5, *B*, *C*, *D*.

The vector determined from the classical leads, by the classical methods (it forms an angle of 65° with D_I and has a magnitude of 20) may be considered approximately the projection of that vector on the frontal plane.

C. *Calculation of the Distances of the Dipoles.*—By measuring the magnitudes of corresponding deflections in B_E and U_W it is possible, as we have seen, to calculate the distances. In Fig. 7*a*, we give some examples, where we have calculated these distances. In each vertical group of two tracings, the upper tracing is a B_E and the other a U_W. For each QRS, we refer to the approximate values of the distances at which are the dipoles, for the maximum of the principal deflections. The leads were obtained at the points α, β and γ, located as indicated in the scheme of Fig. 7*b*. *A* and *A'* were registered at the points α and β in a case with a normal ECG, the tracings *B* at α in a case of complete right bundle branch block, and *C*, *C*,' and C'' in a case of incomplete right bundle

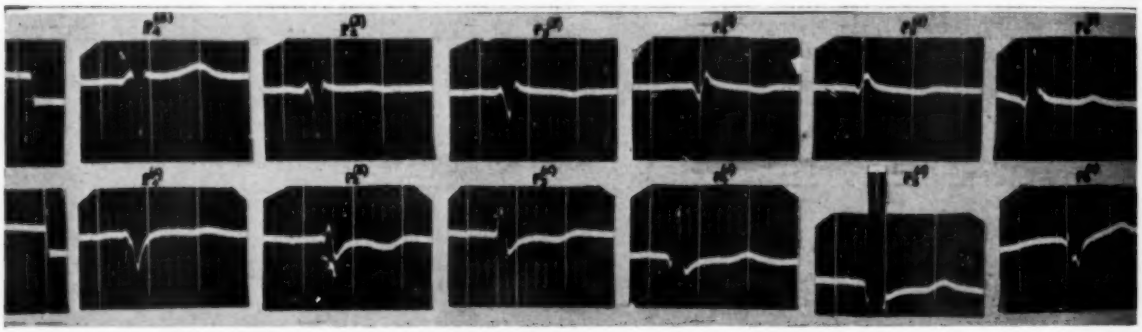


Fig. 6*A*.— α and γ refer to the points of Fig. 7b. The letters *P* and numbers have the same meaning, as in the case of Fig. 5.

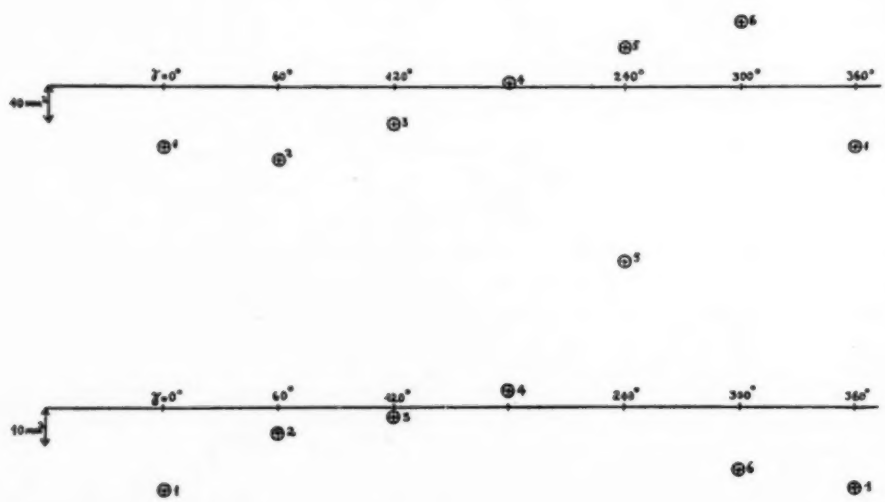


Fig. 6*B*.—Points plotted as in Fig. 5,*C*, corresponding to the two sets of tracings of Fig. 6*A*.

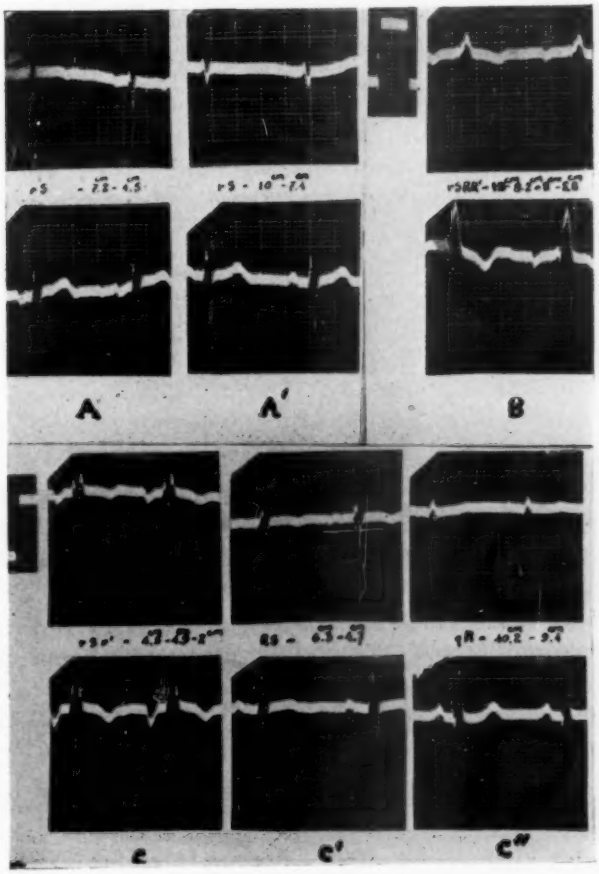


Fig. 7 *a*.

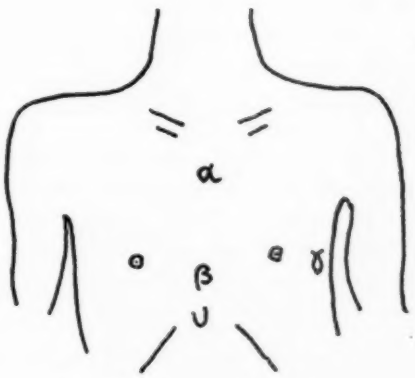


Fig. 7 *b*.

branch block at α, β, and γ, respectively. We must note that, in these cases of right bundle branch block, the least distance we calculated for the dipoles is the distance which corresponds to the R′.

D. *Calculation of the Angles.*—The determination of the angle a of the directions of the leads is simultaneous with that of the distances. For the angles of the planes, we have generally postulated them equal to the angles directly measured. It is a cause of error, that may be minimized, at least in one case. It is the one we consider in the Comment and corresponds to the planes we take as equator and meridians. These planes determine an angle of 90°. As it is possible with unipolars made in such planes (Appendix II) to calculate the vectors, we have here a case where the vectorcardiogram may be theoretically determined, yet with less distortion.

COMMENT

The main objectives we pursued with the investigations from which we have given the principles and some examples (the results assembled until now do not enable us to give statistically valid conclusions) are fundamentally three: (1) to determine the leads that may be considered vectorial; (2) to determine between these vectorial leads which are the best for the construction of the vectorcardiographic curves; (3) for the leads, for instance the precordials, that are not exactly (with a determined approximation) vectorial, to determine their nature or the degree of accuracy, and in what sense they may be taken as vectorial.

Concerning the first objective, it may be observed that the classical and unipolars limb leads are generally considered distant or vectorial. But we must open here a parenthesis for the limb unipolars. For these, a type of interpretation is generalized, based on the theory of the predominant influence of certain cardiac surfaces, in particular when it is to determine the electrical position of the heart. This interpretation has its difficulties, as was pointed out by Johnston and associates.[10] The most evident is the fact that the electrical position may change with the type of the electrocardiogram (for example, when in the same individual a bundle branch block changes from right to left). However, it is possible to explain these facts by the vectorial theory and at the same time the criteria for the determination of the electrical position.[9]

If the vectorcardiogram is a plane (see demonstration in Appendix III) the complexes registered at all the points whose directions of the leads are in the same plane perpendicular to that of the vectorcardiogram are similar. Therefore, it is explained that the limb records may be similar to the precordials, and also the results of Wolferth and associates who verified that it is possible to register similar records along determined directions on the thorax. It is not necessary to admit predominant influences of certain cardiac surfaces or favored transmissions by tissues of better conductivity.

The vectorcardiogram being a plane (which is grossly the case in the normal), the vectorial theory is sufficiently explanatory. It is also understandable that

the electrical position can change radically, as in the case of Johnston and associates[10] (changes in the type of bundle branch block or with any other type of intrinsic change), because then the change is not in the effective position of the heart, but in the plane of the vectorcardiogram. The position may be undetermined, when the vectorcardiogram is clearly far from a plane (infarcts, etc.).

But evidently these considerations do not demonstrate the vectorial nature of the limb unipolars. The best proof of this nature is not quite convincing; this is given, we suppose, by the possibility of obtaining a central terminal with a potential of zero at all times (by summing V_R' V_L, and V_F. However, in the rare cases where a direct evaluation of this potential was made, the value zero was obtained with only an approximation of the order of 0.3 mv. Of course, the possibility of constructing the vectors is not in itself a proof. But the fact that the vectors constructed utilizing other triangles different from those defined by the limb leads are similar to those obtained with the Einthoven triangle is more convincing. With all these leads the respective spatial angles are postulated and not directly measured. (In general, they are supposedly equal to those we may imagine in a Euclidean space where the body would be immersed and without taking into account the structure of the real space corresponding to the electric field in the human body.)

Probably, it is a more suggestive proof of the vectorial nature of the limb leads that " . . . flow lines through the heart found in various leads with the fluid mappers are similar but not identical to the those obtained by use of the Einthoven Triangle concept."[11]

We must recognize that these arguments do not force the conviction of the vectorial nature of the limb leads. For the chest leads, (and in general for all regions where the body is everywhere convex), the method we have presented may give a more convincing answer. This method is, as we have seen, essentially based on the search of relations between the potentials in points of such a region and at a distance sufficiently small in order that it should be conceivable that they are located in an ideal spherical region with a centric dipole. The relations actually observed agree approximately with those deducted for these spherical regions.

These relations are naturally those that enable us to construct vectors and so we are taken to the second problem: the construction of the vectorcardiogram implicates the registering of more than one lead and should not be possible if we cannot measure the distances (or at least demonstrate that for all the leads utilized these distances are the same) and the angles of the directions of the leads. We do not see how this may be made if we lead from points far apart. All that we can do in such a case is, as we have seen for the limb leads, to postulate these distances and angles. But, if the points are near, it is reasonable that they may be at approximately the same distances of the dipoles and we have seen how it is possible to measure the angles. The construction of the vectors is then, and only then, possible.

This is, we believe, the only theoretically rigorous way of determining the vectorial nature of a lead.

In the third objective, the leads naturally implicated are the precordials. For these we have observed deformations of the equivalent tracings in relation to the Wilsonian unipolars. But these deformations, if sometimes notable, in general are not sufficient to change the fundamental pattern and consist essentially in a different attenuation of the various components. These attenuations are functions of the distances at which the dipoles are placed, for they are measured by

$$1 - \cos \frac{D}{d}.$$

This fact suggests immediately a quite simple interpretation, which consists in the admission that, although the cardiac electrical phenomena are not at each point equivalent to a succession of centric dipoles in a sphere of constant radius, at each instance they may be replaced, in general, by a dipole, but at the successive instances the corresponding dipoles must be supposed localized in the space at different places.[9] It is in this sense that we interpret the different values calculated for the distances of the dipoles that correspond to the various deflections of the tracings in Fig. *7a*.

As it is evident, we must know where in relation to the heart the vectors are localized and, in particular, where they must be supposed to be localized

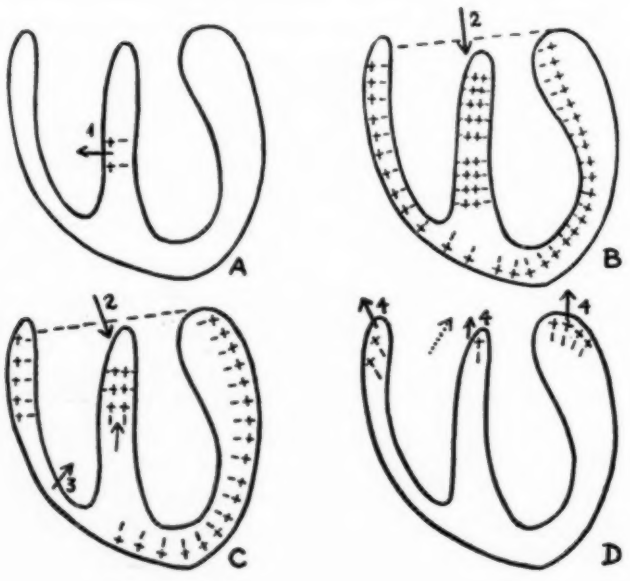


Fig. 8.—*A*, The vector *1* corresponds to the first phase of the ventricular activation: the septal activation. *B*, When, in a second phase, the ventricular walls are activated, the activation wave determines a two-layer surface S and the resultant vector *2* can be defined by the inverse complementary two-layer surface (the complementary surface Σ is such that Σ + S forms a closed surface). This vector *2* must not then, probably, be represented in the left ventricular wall but at the base. (This localization is in accordance, for instance, with the fact that right S waves are often bigger than the left R, in cases of left ventricular hypertrophy.) In a third phase (*C*), is postulated a new complementary vector, on the wall of the right ventricle still activated. During the last phase (*D*), the vectors are basal.

successively in the case of the normal activation. The succession of vectors, presented by Gardberg and Ashman[12] are well known; however, some details of this are not adjustable with results obtained with our method and happily with some fundamental principles almost universally accepted. In fact, the waves of depolarization progressing in the myocardium may be supposedly equivalent to double layers with the charges plus in the forward area. Then, we think it is legitimate to imagine the successive vectors in the normal case as they are represented in Fig. 8.

When for all the leads the vectorial interpretation may be accepted as valid, with a certain approximation, we may reduce the apparent complexity of the electrical cardiac field to an integrated representation within the starting hypothesis. The body substituted by the ideal homogeneous sphere and the electrical intrinsic phenomena is represented, at each instant, by a vector placed at the center of the sphere. The ideal localization of the points where the electrodes are placed is defined by the intersection of the directions that correspond to the leads with the sphere.[9]

In particular, if the vectorcardiogram is a plane, we may take its plane as the equator, and the meridians are determined by the lines of similar records. The angles of the leads are determined as previously described.[9]

As to the extent that the vectorcardiogram is a plane and the precordials are vectorial leads, its value consists essentially in giving us a set of possible patterns of the electrocardiographic curves and this is, with the largest amplitude of the tracings, only verified if they are made in the plane of the vectorcardiogram, so the points of the lead must be chosen in accordance with the position of this plane and therefore broadly with the electrocardiographic position.

Finally, we must observe that our results are dependent on the recording of the unipolars, and the fact that the CT may have a potential different from 0 may alter considerably the final interpretation. We are consequently interested in obtaining a better indifferent electrode. As the value S of the potential of the ring-electrode is 0, when $a = 90°$, we are trying to find such an electrode in this way. But until now we have not a sufficient set of experiences to establish the better ring in every case.

SUMMARY

Starting from the principle that the accuracy of the vectorial interpretation of the electrocardiographic tracings must be ascertained in each individual and is only established when the vectors may be constructed, the conditions of this construction were logically determined.

It is shown that all the points for the leads (more than one point is obviously necessary) must be located on a continuous convex region of the surface of the body with a spherical electrical symmetry.

In such a region, first, the difference of potential between a point P on the thorax and points P_i equidistant from P is a sinusoidal function of the angle defining the position of the points P_i and, second, the difference of potential

between the point P and a conducting ring including all the points P_i is proportional to the potential at P. The degree with which the first condition is verified may be measured by a correlation coefficient, and the second condition implies that the tracing so obtained must be similar to the unipolar at P, and the quotient of the amplitudes of the two tracings at each instant is a function of the distance of the dipole to the point P. It is supposed that the vectorial interpretation is valid when that correlation coefficient is approximately equal to 1 (or, more practically, when a sinusoidal curve is approximately obtained with the differences of potential measured as referred to in the first condition), and the calculated distances are the same for the dipoles of a cardiac cycle. Methods are given for the calculation of the vectors and the construction of the vectorcardiogram in this case.

When the calculated distances are different during the cardiac cycle, they still may determine the spatial localization of the successive dipoles.

As the limb leads do not satisfy the conditions of applicability of the methods proposed, it is not possible for them to offer new proofs of their vectorial nature in this way.

But it is shown that, particularly the kind of nonvectorial interpretation of the limb unipolars which is associated with the usual definitions of the electrical positions of the heart, is not necessary. These definitions are compatible with the vectorial interpretation; the similarity of the patterns of the precordials and those of the limb leads are probably in relation to the fact that the vectorcardiogram is normally approximately a plane.

When a vectorial interpretation of the tracings is valid for all the current leads, the ideal sphere equivalent to the human body may be determined.

Finally, we justify the opinion that the points for the precordial leads must be chosen in accordance with the electrical position, and a new principle for an indifferent electrode is presented.

SUMMARIO IN INTERLINGUA

Es presupponite le hypotheses del quales depende le validitate del interpretation vectorial del traciamentos electrocardiographic. Super iste base es deducite relationes mathematic que debe esser satisfacite per le differentias de potential inter un puncto e altere punctos equidistante ab illo intra un parve region thoracic. Es demonstrate que le differentia de potential registrate inter un electrodo circular in le puncto P e un anulo concentric es proportional al potential del electrodo central de maniera que le bipolares assi obtenite debe esser morphologicamente simile al unipolares in P.

Ille constante de proportionalitate permitte le calculation del distantia a que le dipolo se incontra ab P.

Le grado a que iste relationes theoric es verificate es un mesura del grado de approximation con que vectores pote esser construite.

Es verificate que le traciamentos registrate in alicun individuos satisface iste relationes e que le vectores pote esser construite.

Le criterios wilsonian pro le determination de positiones electric es integrate in le theoria vectorial e le signification del precordiales es discutite.

APPENDIX I

The set of hypothesis made is that of the dipole centric in a sphere with a radius sufficiently big, for the potential at each point on the surface to be $V = K \cos \Theta$. In Fig. 1 the dipole is supposedly with the charge negative at the center of the sphere and with its axis intersecting this sphere at N and points P_i at equal distance a from P.

If it is observed that in the spherical triangle (NPP_i)

$$\cos \Theta = \cos \Theta \times \cos a + \sin (\Theta) \sin a \cos \alpha_i,$$

we may write:

$$V_{P_i} - V_P = K (\cos \Theta_i - \cos \Theta) = S + T \cos \alpha_i$$

with

$$S = K \cos \Theta (\cos a - 1) \text{ and } T = K \sin \Theta \sin a.$$

(The letters Θ, α, and a represent angles evident in Fig. 1.)

Consequently,

For each dipole, each P and constant distances a of the points P_i, S, and T are constant and the differences of potential $V_{P_i} - V_P$ are linear functions of $\cos \alpha_i$.

If we register the differences of potential between a fixed point P (for instance on the thorax) and equidistant points P_i, the directions P_iP make with the direction $\overline{P_iP}$ an angle $\gamma_i = \alpha_i + \beta$. The value of β and consequently the α_i corresponding to each γ_i may be determined if we trace the curve.

$$V_{P_i} - V_P = S + T \cos \alpha_i = S + T \cos (\gamma_i - \beta) = f (\gamma_i).$$

This curve must be sinusoidal and has a maximum value $= S + T$ (T is always positive because $\Theta < 180°$ and a is also chosen $< 180°$). For this maximum $\alpha_i = 0$. The corresponding value of $\gamma = \gamma_M = \beta$.

If the hypothesis is valid the function $V_{P_i} - V_P = f(\cos \alpha_i)$ must be represented by a straight line. The distribution of points (α_i, $V_{P_i} - V_P$) should theoretically enable us to determine the values of S and T and a correlation coefficient measuring the degree of validity of the hypothesis.

As practically the number of points (α_i, $V_{P_i} - V_P$) that we determine is not sufficient to give enough credit to the statistical values so found, we prefer for the evaluation of S and T the method we give with the example in the text (case of Fig. 5).

For the value of S we may remark that according to the relation

$$V_{P_i} - V_P = S + T \cos \alpha_i$$

the value of the difference of potential between a conductor ring including all the points P_i and P is evidently the mean value

$$V_R - V_P = \frac{1}{2\pi} \int_0^{2\pi} (V_{P_i} - V_P)\, d\alpha = S$$

V_R representing the potential $K \cos \Theta \cos a$ of the conductor ring.

It must be observed that the potential of the ring (which would theoretically form a zero potential terminal for $a = 90°$) is proportional to the potential $V_P = K \cos \Theta$ and the quotient, $\frac{V_P - V_R}{V_P} = 1 - \cos a$, enables us to calculate a and consequently for a distance D measured between the points P and P_i, the radius d of the sphere ($a = \frac{D}{d}$).

(According to the polarity chosen the bipolar equivalent we register $B_E = V_P - V_R = -S$.)

APPENDIX II

If we chose three points P, P_1 and P_2 (Fig. 9) on an electrical spherical region, P_1 and P_2 at the distance a from P and so that the circles of P_1 and P_2 are orthogonal, if the point of intersection of the direction of the dipole with the sphere is at N_1, then

$$\cos \Theta' = \cos \Theta \cos a + \sin \Theta \sin a \cos \alpha$$
$$\cos \Theta'' = \cos \Theta \cos a + \sin \Theta \sin a \sin \alpha.$$

If U, U′, and U″ are the amplitudes of the unipolars at P, P_1, and P_2, respectively, we can write

$$U' = U \cos a + T \cos \alpha$$
$$U'' = U \cos a + T \sin \alpha.$$

And if a is known, we know $U' - U \cos a = F$ and $U'' - U \cos a = G$, and therefore it is possible to calculate T and α, and therefore the magnitude and the direction of the dipole.

As T is obviously always positive, the signs of F and G determine the position of N, in relation to the coordinate curves PP_1 and PP_2.

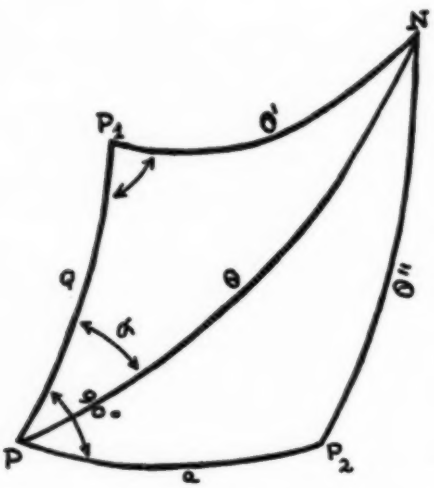


Fig. 9.

APPENDIX III

Let the components of a real vector referred to a set of rectangular axes with origin at the origin of the vector be X, Y, and Z, the direction cosines of the leads at two points C and C′ be (α, β, γ) and $(\alpha', \beta', \gamma')$ respectively, and the potentials measured at the points be m and m′. It can be written

$$m = \lambda (\alpha X + \beta Y + \gamma Z)$$
$$m'' = \lambda' (\alpha' X + \beta' Y + \gamma' Z).$$

λ and λ' are constants.

If the curves we register at the two points are similar,

$$\frac{\lambda [\alpha X(t) + \beta Y(t) + \gamma Z(t)]}{\lambda' [\alpha' X(t) + \beta' Y(t) + \gamma' Z(t)]} = \text{Constant (independent of the time).}$$

Putting $\frac{\lambda'}{\lambda} \times \text{Constant} = K$

$$\alpha X + \beta Y + \gamma Z = K\alpha' X + K\beta' Y + K\gamma' Z$$

If X, Y, and Z are quite independent, this condition imposes

$$\frac{\alpha}{\alpha'} = \frac{\beta}{\beta'} = \frac{\gamma}{\gamma'} = K$$

and as $\alpha_2 + \beta_2 + \gamma_2 = 1$ and $\alpha'_2 + \beta'_2 + \gamma'_2 = 1$

$$K = \pm 1$$

There is, for each point, only another point, for which the condition is verified (a point which gives a mirror pattern).

But, if we suppose

$$Z = aX + bY$$

it must be

$$\alpha + \gamma a = k\,(\alpha' + \gamma' a)$$
$$\beta + \gamma b = K\,(\beta' + \gamma' b)$$

and also,

$$\beta a - b\alpha = K\,(\beta' a - b\alpha')$$

and therefore,

$$p_1 = b\gamma + \beta = K\,(b\gamma' + \beta')$$
$$p_2 = -\alpha - a\gamma = K\,(-\alpha' - a\gamma')$$
$$p_3 = a\beta - b\alpha = K\,(a\beta' - b\gamma').$$

p_1, p_2, and p_3 are components of a vector perpendicular to the plane defined by (a, b, −1) and (α, β, γ) and also to that defined by (a, b, −1) and $(\alpha', \beta', \gamma')$, which signifies obviously that (α, β, γ) and $(\alpha', \beta', \gamma')$ are on the same plane perpendicular to the plane $aX + bY - Z = 0$.

Thanks are due to Prof. A. Cordeiro, Lisbon University, for helpful criticism.

REFERENCES

1. Einthoven, W., Fahr, G., and de Waart, A.: Ueber die Richtung und manifeste Grösse der Potentialschwankungen in menschlichen Herzen und über den Einfluss der Herzlage auf die Form des Elektrokardiogramms, Pflügers Arch. **150**:275, 1913.
2. Schellong, F., Heller, S., and Schwingel, E.: Das Vectorkardiogramm, eine Untersuchungsmethode des Herzens, Ztschr. Kreislaufforsch. **29**:497, 1937.
3. Wilson, F. N., and Johnston, F. D.: The Vectorcardiogram, Am. Heart J. **16**:14, 1938.
4. Duchosal, P. W., and Sulzer, R.: La Vectorcardiographie, Basel, 1948, S. Karger.
5. Grishman, A., Borun, E. R., and Jaffe, H. L.: Spatial Vectorcardiography: Technique for the Simultaneous Recording of the Frontal, Sagittal, and Horizontal Projections, Am. Heart J. **41**:483, 1951.
6. Bürger, H. D., and van Milaan, J. B.: Physical Foundations of Vectorcardiography, Communications du ler Congrès Mondial de Cardiologie **1**:545, 1951.
7. Moreira, J. A.: Derivações próximas e a distancia. I. Método para a sua discriminação pelo estudo regional do torax humano com derivações bipolares, Clin. Contemp. **6**:116, 1952.
8. Moreira, J. A.: Derivações proximas e a distancia. II. Construção de um vectorcardiograma correcto a partir de derivações toracicas unipolares regionais, Clin. contemp. **7**:41, 1953.
9. Moreira, J. A.: Derivações proximas e a distancia. III. Interpretação vectorial das derivações electrocardiográficas correntes, Clin. Contemp. **8**:79, 1954.
10. Johnston, F. D., Ryan, J. M., and Bryant, J. M.: The Electrocardiogram and the Position of the Heart, Am. Heart J. **43**:306, 1952.
11. McFee, Richard: Graphic Representation of Electrocardiographic Leads by Means of Mappers, Circulation **6**:21, 1952.
12. Gardberg, M., and Ashman, R.: QRS Complex of Electrocardiogram, Arch. Int. Med. **72**:210, 1943.

THE VECTOR-ELECTROCARDIOGRAM IN ACUTE CORONARY INSUFFICIENCY AND IN ACUTE MYOCARDIAL INFARCTION

R. S. Cosby, M.D., J. C. Talbot, M.D., D. C. Levinson, M.D., and Mary Mayo, B.A.

Los Angeles, Calif.

INTRODUCTION

THE ability of the electrocardiogram to record the changes of acute transmural myocardial infarction is well recognized. There is, however, a considerable difference of opinion in regard to the detection by this method of lesser degrees of myocardial injury. Such clinical states have been variously labeled as: (1) acute coronary insufficiency,[1] (2) coronary failure,[2] and (3) subendocardial infarction.[3] In the few reports of cases with autopsy verification,[3-6] the pathology has consisted of areas of myocardial necrosis, usually subendocardial, with or without coronary artery occlusion.

The electrocardiographic and clinical criteria of acute myocardial infarction are well defined: the appearance of abnormal Q waves or QS complexes along with reciprocal S-T deviation, associated with persistent substernal pain. However, when acute substernal pain is associated with S-T depression and T-wave inversion, without abnormal Q or QS complexes and usually without reciprocal S-T deviation, acute coronary insufficiency is presumed to be present. The incidence, pathologic features, severity, clinical course, and prognosis of acute coronary insufficiency need further definition and study.

This paper represents an attempt to evaluate the clinical differences between acute coronary insufficiency and acute myocardial infarction, and the electrocardiographic differences by means of vector electrocardiography (mean spatial vectorcardiography).

MATERIAL AND METHODS

Clinical Material.—The subjects of this investigation were twenty-seven patients with acute myocardial infarction and twenty-four patients with acute coronary insufficiency who were seen in private practice over the past four years.

From the Department of Medicine (Cardiology), University of Southern California School of Medicine, and the Los Angeles County Hospital, Los Angeles, Calif.

Read at the Clinical Session, American Heart Association Scientific Sessions, Chicago, Ill., April, 1954.

Received for publication Nov. 23, 1954.

In the latter group, the clinical picture resembled that of acute myocardial infarction, but the symptoms were milder and the illness of shorter duration. Although the actual anatomic lesion was not identified, it was felt that in the majority of cases subendocardial infarction was present. All of the cases were selected only on the basis of the availability of several 12-lead electrocardiograms during and subsequent to the acute episode. The patients have been followed for periods of from six months to four years each. A total of 300 electrocardiograms were studied in the fifty-one patients.

Vector Methods.—At any given instant in the cardiac cycle, the direction and magnitude of the electrical force of the heart may be represented by a single straight line in space, or instantaneous spatial vector. This instantaneous vector changes in magnitude and direction during the events of each cardiac cycle. If the successive instantaneous spatial vectors are represented during the QRS part of the cardiac cycle as arising from a single point, the electrical null point of the heart, and then if the ends of these vectors are joined, the result will be a closed curve, the so-called QRS loop. The vectorcardiogram is an oscilloscopic projection of this loop in the frontal, horizontal, and sagittal planes. It is possible, from the characteristics of the loop in two planes, to construct a wire model of the three-dimensional or spatial loop. However, the spatial vectorcardiograph in its present form has definite limitations. The important T phase of the cycle is often not well shown; and the records obtained cannot be readily measured and must be described mainly in nonquantitative terms. It is for these reasons that mean spatial vectorcardiography was chosen for the study of the electrocardiograms selected.

The vector approach can be greatly simplified by considering mean instead of instantaneous vectors.[7] All the instantaneous vectors during the QRS cycle are replaced by a single mean QRS vector, representing the average direction and magnitude of the QRS forces; the mean T vector shows the average forces during the T phase of the cycle. The complex patterns of the multiple-lead electrocardiogram are thus replaced by two vectors, each defined by its magnitude and direction in space. Some features of the electrocardiogram are of course lost in this simplification; this method, often termed vector-electrocardiography, cannot replace conventional methods of interpretation. This paper will illustrate its usefulness in clinical investigation.

The mean QRS and T spatial vectors can readily be derived from the conventional 12-lead electrocardiogram. The familiar procedure of finding the QRS axis from Einthoven's triangle constitutes the first step. The mean amplitude of the QRS complex in standard Leads I and III is measured, and from this a line is plotted which shows the magnitude and direction of the mean QRS vector as projected on the frontal plane. Then, to define the vector completely as it is oriented in space, the direction of its projection on the horizontal plane is determined. This is done from the precordial lead complexes; the vector will be directed toward the positive complexes, and in a direction perpendicular to the lead in which the QRS complex is equally positive and negative.

Simonson's spatial vector analyzer[8] is an ingenious device which aids in visualizing the mean spatial vectors of QRS and T in space. In this device, a

steel ball is fixed above the center of a baseboard. The vectors are represented by metal rods attached to small magnets, which can be moved about on the ball so as to indicate any position of the vector. The vector rods are graduated so that the length (magnitude) of a particular vector may be readily determined.

The direction of a vector is defined by two angles: the horizontal angle which indicates its direction in the horizontal plane, and the vertical angle. The vertical angle is the angle between the vector and a perpendicular dropped from the center of the heart. Thus the vertical angle is always positive from 0° (directly downward) to +180° (directly upward). The horizontal angle is measured from 0° on the left to +180° on the right, with the positive hemisphere in front and the negative hemisphere behind.

The requisite information for the determination of the horizontal angle is the accurate definition of the transitional zone in the precordial leads. To facilitate this, Simonson and Keys[9] and Milnor and associates[10] employed a modification of the usual precordial leads, taking Leads V_1, V_2, and V_3 at the same level as Leads V_4, V_5, and V_6. When these leads do not include the transitional zone, either for QRS or for T, additional electrode positions to the right of Lead V_1 are used. Since the present study was retrospective, Simonson's analyzer had to be applied to the conventional 12-lead electrocardiogram. According to Simonson,[8] this involves a relatively small error in the determination of the mean spatial vector, especially in abnormal cases.

Actual spatial angles of the QRS and T vectors were recorded separately, rather than the composite QRS-T angle. The QRS-T angle would probably be more useful in the interpretation of an isolated tracing, but the separate angles seem to show the dynamic changes in acute myocardial infarction or acute coronary insufficiency to better advantage. Also, emphasis on the individual spatial angles illustrates the differences in injuries to various sites in the heart, differences which are obscured when only the QRS-T angle is considered.

In this study only the QRS vectors and the T vectors are reported. These are mean vectors in time, since the QRS complex and the T wave with the S-T segment are replaced by single vectors. Some important features of the electrocardiogram are therefore omitted; the S-T segment as such is not represented in the vector, and the Q wave cannot be easily singled out as a separate entity. In addition, vectors can be determined for the S-T segment only in tracings with marked S-T deviation. Such changes are rare in this series of cases with acute coronary insufficiency and are usually transient in the tracings with myocardial infarction.

RESULTS

Clinical Course.—There were twenty-four patients with acute coronary insufficiency, averaging 58.1 years of age; eighteen of these were male, six were female. There were twenty-seven patients with acute myocardial infarction. Their average age was 55.6 years; twenty were male, seven were female.

In acute coronary insufficiency, the precipitating factors were not often well defined. Seventeen of the twenty-four patients developed acute coronary

insufficiency of whom three later had an acute myocardial infarction. In contrast, three patients developed acute pulmonary edema prior to coronary insufficiency; three more were in mild failure from hypertensive heart disease and one had severe anemia.

The clinical course was less severe in acute coronary insufficiency than in myocardial infarction. No patients were in shock. Failure did not occur except in the six patients who already had pulmonary edema or hypertensive heart disease. The failure was mild and/or temporary in all six cases. In nine patients pain was severe and prolonged. The average stay in the hospital for acute coronary insufficiency was ten days in comparison with eighteen days for myocardial infarction. Three-fifths of the patients with acute coronary insufficiency had elevated white counts; the white counts were on the average far higher in acute myocardial infarction. Following the acute episode in coronary insufficiency, five had residual attacks of angina; five were on digitalis and seven were well. No patient died during the acute episode; there were, however, three deaths subsequently from heart disease. In the twenty-seven patients with acute myocardial infarction there were four deaths. Six patients had angina following their attack, and six patients had congestive failure during the attack of myocardial infarction. In all cases convalescence was more prolonged than in acute coronary insufficiency.

Electrocardiograms.—

A. *General:* In acute myocardial infarction, the anterior surface of the heart was affected in eleven patients (six anteroseptal, two anterolateral, and three anterior); the lateral surface alone was affected in one patient; the posterior and lateral surfaces were affected in four, and the posterior and anterior surfaces were affected in four others; three had purely posterior infarctions and four had both a posterior and an anterior infarction in succession. (See Table I; latter four patients not listed, however.)

In acute coronary insufficiency, the anterior surface of the heart was affected in eighteen patients (nine anteroseptal, eight anterolateral, one widespread anterior); the lateral surface alone in two patients, the posterior and lateral surfaces in one, and the posterior and anterior surfaces in three patients (See Table I).

B. *The QRS vector in myocardial infarction:* In anterior and anteroseptal myocardial infarction the QRS vector shifted laterally and posteriorly in the horizontal plane. The development of Q waves in Leads V_1, V_2, V_3, and V_4, usually with a decrease in the height of R, resulted in a shift of the precordial transition which was reflected in the lateral and posterior shift in the horizontal plane. The shifts were not marked, except in an occasional patient with the loss of R waves through Lead V_4. The shift in the vertical plane was minimal in the anteroseptal group with one exception but was more marked in two of the three patients in the "straight anterior" group. In the two patients with anterolateral infarction, the vertical QRS angle shifted downward due to the appearance of small Q waves in standard Lead I.

TABLE I. A COMPARISON OF VECTOR-ELECTROCARDIOGRAPHIC ANGLES IN CORONARY INSUFFICIENCY AND MYOCARDIAL INFARCTION

CORONARY INSUFFICIENCY

LOCUS	AGE	SEX	Q				T				TIME (DAYS)	
			HORIZ.		VERT.		HORIZ.		VERT.			
			M.A.*	V.S.†	M.A.	V.S.	M.A.	V.S.	M.A.	V.S.	WORST	BEST
ANT. SEPT.	65	M	−12	+6	92	+8	−68	−23	88	+58	1	42
	78	M	−27	−12	77	−19	−79	−109	57	+29	1	28
	65	F	−36	+14	23	−17	−68	−108	45	+10	1	42
	54	F	−52	−6	33	−16	−125	−77	7	−58	2	28
	55	F	+10	−2	90	+5	−145	−157	73	+8	7	40
	70	M	+55	0	85	0	−77	−22	68	+3	1	120
	61	M	−31	−4	64	−4	−110	−113	49	+21	5	90
	52	F	−50	−13	16	−80	−90	−143	72	+15	1	30
	49	M	−37	−10	53	−7	−68	−123	15	+7	4	28
ANT. LAT.	52	M	−10	0	87	+1	+90	+35	4	−54	1	10
	66	F	−38	−20	87	+3	+72	+2	70	−15	1	14
	65	M	−18	−8	27	+1	+79	+37	72	+44	12	140
	48	M	+12	0	97	+2	+150	+95	63	+33	7	90
	55	M	−46	+17	105	+9	+132	+7	80	−5	6	30
	49	M	−38	−20	25	−16	+144	+89	55	+10	8	120
	68	M	−10	−2	53	−15	+70	+17	25	−36	7	54
	53	M	−10	+17	73	−20	+154	+81	76	−12	1	I‡
ANT.	62	F	−42	−2	77	0	−110	−125	67	+4	2	I
P.L.	43	M	−57	−7	68	+7	+54	−1	105	+42	2	75
LAT.	68	M	−3	+15	60	+3	+68	+7	30	−25	1	90
	55	M	−47	−16	73	+1	−38	−67	20	−20	4	95
POST. AND ANT.	57	M	−20	0	107	+15	+172	+27	25	−37	2	21
	59	M	−28	+14	14	+4	+72	+17	75	+10	10	90
	45	M	−75	−15	54	+12	+55	0	8	−13	13	30

*M.A. = Most abnormal vector angle. Note that the vertical angles have no plus or minus sign.
†V.S. = Vector shift from most normal to the most abnormal position.
‡I = Indeterminate.

TABLE I. A COMPARISON OF VECTOR-ELECTROCARDIOGRAPHIC ANGLES IN CORONARY INSUFFICIENCY AND MYOCARDIAL INFARCTION (CONT'D)

MYOCARDIAL INFARCTION

LOCUS	AGE	SEX	Q				T				TIME (DAYS)	
			HORIZ.		VERT.		HORIZ.		VERT.			
			M.A.*	V.S.†	M.A.	V.S.	M.A.	V.S.	M.A.	V.S.	WORST	BEST
ANT. SEPT.	60	M	−57	−10	63	−32	−115	−155	52	+74	28	150
	61	M	−68	−23	35	−8	−108	−145	25	−20	6	365
	49	F	−100	−45	100	−12	−127	−199	70	+17	20	120
	60	M	+38	−9	10	−8	−70	−12	58	+15	7	I
	57	M	−65	−35	50	−12	−137	−192	38	−19	6	I
	49	M	−53	−36	65	+7	−108	−42	35	0	6	42
ANT.	59	M	−70	−40	73	+51	−165	−219	98	+48	22	I
	50	M	−70	−40	75	+53	−120	−190	26	−28	I	116
	53	M	−37	−27	88	+11	−165	−70	61	+56	14	I
ANT. LAT.	50	F	+55	+2	87	−20	+144	+111	5	−25	1	365
	60	F	+70	+5	4	−32	+145	+135	60	+14	20	75
LAT.	53	M	+35	−141	110	−70	+109	+63	72	−37	15	190
POST. LAT.	45	M	−55	−10	80	+7	+50	+30	120	+40	16	120
	61	F	−10	−42	50	+16	+60	+5	128	+68	20	120
	52	M	−28	−15	100	11	+90	+18	150	+143	6	35
	56	M	−47	−37	80	+42	+77	+7	115	+10	10	135
ANT. AND POST.	67	M	−75	−7	110	+14	−75	−145	106	+34	3	90
	62	M	0	−33	98	+18	+10	+38	126	+66	6	150
	55	F	−35	−25	102	+14	−115	−170	57	+12	1	170
	64	M	−61	−19	112	+9	+137	+67	125	+58	14	165
POST.	45	M	−12	−2	112	+30	+55	0	135	+80	14	91
	55	F	+5	−7	70	+7	+70	+30	105	+35	I	98
	55	M	+12	+30	108	+44	+72	+14	139	+74	1	5

*M.A. = Most abnormal vector angle. Note that the vertical angles have no plus or minus sign.
†V.S. = Vector shift from most normal to the most abnormal position.
‡I = Indeterminate.

In patients with posterior myocardial infarction, significant shifts occurred in both the vertical and horizontal vectors of QRS. The vector shift was always upward in the vertical plane and was due to the development of Q waves in standard Leads II and III. However, the horizontal angle of QRS was often affected, indicating the frequency of involvement of the anteroseptal or anterolateral surface of the heart in most posterior infarctions.

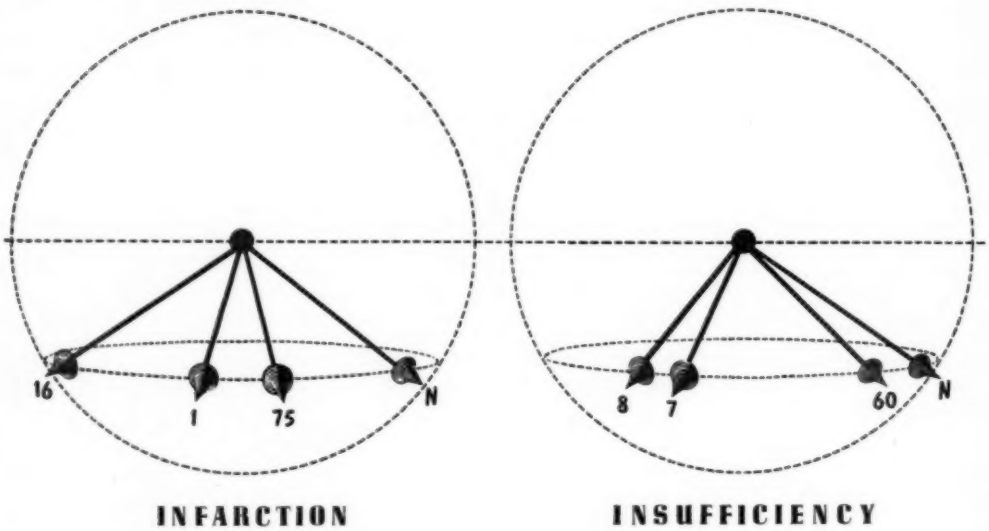


Fig. 1.—T Vectors in anterolateral involvement (Numbers indicate days after onset).

C. *The T vector in myocardial infarction:* Shifts in the T vector were more characteristic and more pronounced than in the QRS vector. In anteroseptal and anterior myocardial infarction the T vector shifted to an extreme degree in the horizontal plane (Table II). Both the most abnormal positions and the vector shifts are far beyond the normal standards set up by Simonson and Keys[9], where the normal horizontal angle for healthy middle-aged males fell between +15° and +70°, and the normal vertical angle fell between 20° and 95°. In myocardial infarction, the T vector appears to turn away from the site of infarction, moving around the lateral surface of the heart to a posterior position (Fig. 1). In the recovery phase, the vector appears to take a similar pathway in the reverse direction. In the two patients with anterolateral infarction, the T vector passes in exactly the opposite direction in the horizontal plane, mainly anterior and toward the septal surface of the heart. In fact, the most abnormal position of the T vector is directly opposite the infarcted area. With respect to the pathway of the vertical angle of T, there is no consistent pattern.

TABLE II. AVERAGE T AND QRS VECTORS IN CORONARY INSUFFICIENCY AND MYOCARDIAL INFARCTION

LOCATION	PLANE	AVERAGE T VECTORS			
		CORONARY INSUFFICIENCY		MYOCARDIAL INFARCTION	
		M.A.*	V.S.†	M.A.	V.S.
Anteroseptal	Horiz.	−92	−97	−111	−124
	Vert.	53	+10	46	+8
Anterolateral	Horiz.	+111	+45	+145	+123
	Vert.	56	−4	32	−5
Posterolateral	Horiz.	+54	−1	+69	+20
	Vert.	105	+42	128	+65
Posterior and anterior	Horiz.	+99	+15	−11	−53
	Vert.	36	−13	104	+43

LOCATION	PLANE	AVERAGE QRS VECTORS			
		CORONARY INSUFFICIENCY		MYOCARDIAL INFARCTION	
		M.A.	V.S.	M.A.	V.S.
Anteroseptal	Horiz.	−20	−3	−51	−26
	Vert.	59	−14	54	−11
Anterolateral	Horiz.	−20	−2	+63	+4
	Vert.	69	−4	46	−26
Posterolateral	Horiz.	−57	−7	−35	−26
	Vert.	68	+7	78	+19
Posterior and anterior	Horiz.	−41	0	−43	−21
	Vert.	58	+10	105	+14

*M.A. = Most abnormal vector angle. (Vertical angles have no plus or minus sign.)
†V.S. = Vector shift from most normal to the most abnormal position.

In posterior myocardial infarction, the T-vector shift was primarily in the vertical plane (See Table II). This vector shifted upward (Fig. 2) due to the marked inversion of T in classical Leads II and III. Shifts in the horizontal

angle of T were variable, depending on whether or not the anterior surface of the heart was affected. Two patients, for example, shifted 145° and 170°, respectively, in their horizontal angles of T, due to T-wave inversion in the right precordial leads.

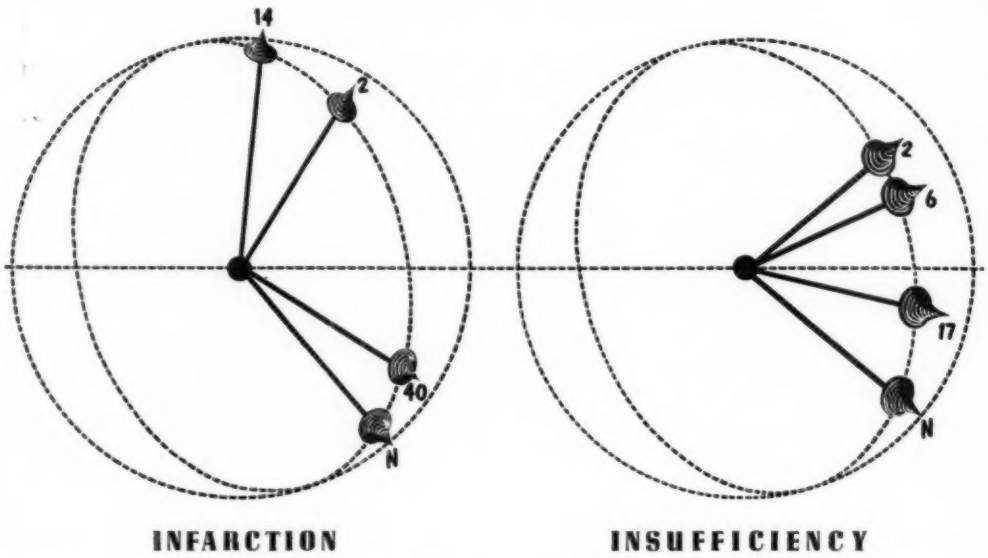


Fig. 2.—T Vectors in posterior involvement (Numbers indicate days after onset).

D. *Clinical correlation:* The relation of the severity of the illness to the maximum T-vector shift in the two largest groups of cases with myocardial infarction, anteroseptal and posterior, is shown in Table III. A striking relationship was evident in the anteroseptal group, and no relationship at all was shown in posterior myocardial infarction. Essentially, the greater the shift in the horizontal angle of T in anteroseptal infarction, the more widespread was the inversion of the precordial T waves.

No correlation between severity of illness and the T-vector shift was possible in acute coronary insufficiency, since the illness was uniformly moderate rather than severe.

E. *The QRS vector in acute coronary insufficiency:* Since by definition the patients with acute coronary insufficiency developed no abnormal Q waves or QRS complexes, the horizontal or vertical shifts in the QRS vector were entirely attributable to changes in the axis. These shifts were minimal in every case except in one patient who had an increasing vertical angle of 80° due to the development of right bundle branch block as a manifestation of acute coronary insufficiency. Two other patients who developed left bundle branch block in the course of acute coronary insufficiency showed no particular vector shift.

TABLE III. RELATION OF THE MOST ABNORMAL T VECTOR TO CLINICAL STATUS IN ANTEROSEPTAL AND POSTERIOR INFARCTS

ANTEROSEPTAL AND ANTERIOR INFARCTION		POSTERIOR INFARCTION	
HORIZONTAL T VECTOR	SEVERITY OF ATTACK	VERTICAL T VECTOR	SEVERITY OF ATTACK
−165	Severe	150	Mild
−165	Severe	139	Severe
−137	Severe	135	Severe
−127	Severe	128	Severe
−120	Moderate	126	Moderate
−115	Moderate	125	Moderate
−108	Moderate	120	Severe
−108	Mild	115	Severe
−70	Mild	105	Moderate
		105	Severe

F. *The T vector in acute coronary insufficiency:* The shifts in the T vector in acute coronary insufficiency were not as pronounced as those in myocardial infarction. The pathway of the T vector was the same in both; the vector was directed away from the injured area. For example, when coronary insufficiency involved the posterior surface of the heart, the abnormal T wave was directed upward (Fig. 2). The extent of the shift of the T vector was less than in acute myocardial infarction. The mean shift of the horizontal T vector was 124° in anteroseptal infarction, and was 97° in acute anteroseptal coronary insufficiency, as can be seen in Table II.

G. *S-T changes in acute coronary insufficiency and in acute myocardial infarction:* As expected, shifts in the S-T segment were minimal in acute coronary insufficiency compared to those in myocardial infarction. S-T depression without reciprocal S-T elevation was present in eleven out of twenty-four patients with coronary insufficiency. In those patients, S-T depression in the precordial leads and in Lead I was a conspicuous and important feature of anterior coronary insufficiency and did not occur in anterior myocardial infarction. Four patients with coronary insufficiency did have reciprocal S-T deviation, attributable to bundle branch block in three and to minimal left ventricular hypertrophy in one. In two patients out of twenty-four, reciprocal S-T deviation was apparently a feature of the acute coronary insufficiency itself. Seven patients had no S-T changes at all in the electrocardiograms available.

The S-T segment changes in acute myocardial infarction were invariably reciprocal, emphasizing again the uniformity, as well as specificity, of the electrocardiographic changes in acute myocardial infarction.

H. *Return to normal—coronary insufficiency and myocardial infarction:* An important difference between acute myocardial infarction and coronary insufficiency was in the time at which the maximum shift in the T vector took place. In coronary insufficiency this happened on the third or fourth day, rather than on the tenth or eleventh day, as in infarction. Also, the electrocardiogram stabilized earlier than in myocardial infarction. In coronary insufficiency, the electrocardiogram stabilized on the average in 59 days; it took on the average 137 days for the electrocardiogram to stabilize in myocardial infarction. Electrocardiograms in few patients in either group returned completely to normal; there were seven completely normal electrocardiograms in the coronary insufficiency group after recovery from the attack; and only four in the group with acute myocardial infarction.

DISCUSSION

Reference has been made to the wide diversity of opinion that exists as to the incidence, pathologic features, severity, clinical course, and prognosis in acute coronary insufficiency. Each of these points will be discussed in turn.

The frequency of acute coronary insufficiency compared to the frequency of acute myocardial infarction is most difficult to determine. Master,[1] in 1951, reported on 412 patients with acute myocardial infarction and 147 patients with acute coronary insufficiency. He admitted, however, that his series were comprised of primarily " . . . severely ill patients, most of whom were seen only once in consultation." In another series of 143 patients reviewed from a pathologic standpoint by Miller and associates[6] 66 per cent had coronary occlusions and 34 per cent were without coronary occlusions, most of the latter being "primarily subendocardial." The literature on individual cases of acute coronary insufficiency is indeed scarce. Prinzmetal and associates[11] in a review of the medical literature could discover only eleven patients described by Pardee and Goldenburg,[12] forty patients described by Myers and associates,[13-15] six described by Levine and Ford,[3] and ten gathered from the literature by Lepeschkin.[16] To these might be added the seventy cases of Papp and Smith,[5] primarily clinical, and the twenty-three cases of Yu and Stewart,[4] seven with autopsy correlation. It is remarkable that so few cases have been reported during the past ten years.

The group of cases presented in this paper, being a selected series, is not to be considered representative of the relative incidence of the two conditions. We would agree with Prinzmetal and associates[11] however, that the " . . . actual incidence of pure subendocardial infarction is greater than indicated by available clinicopathologic data," and would judge, from the combined series of Master and Jaffe[1] and Miller and associates,[6] that it might be well to consider it at least half as common as acute transmural myocardial infarction.

It seems significant that interest in acute coronary insufficiency has grown considerably since precordial leads have become routine. This may well be related to the predominance of anterior over posterior involvement, more striking in acute coronary insufficiency than in myocardial infarction. In a series of thirty-five patients described by Papp and Smith[5] as "slight" myocardial in-

farction, (ST-T changes without the appearance of abnormal Q waves), only 25.7 per cent were posterior in location. In the seven autopsy-proved cases of Yu and Stewart,[4] five were anterior subendocardial in location, and all of the sixteen nonautopsied cases were anterior and subendocardial. In the series of Levine and Ford,[3] all patients showed involvement of the anterior and subendocardial surface, and no mention was made of the possibility of injury to the posterior surface. In the patients reported by Miller and associates,[6] 76 per cent of the cases with acute coronary insufficiency were anterior, and only 22 per cent were posterior. They pointed to " . . . the greater degree of narrowing of the anterior descending coronary artery" as an explanation for the more frequent involvement of the anterior surface in coronary insufficiency. It should be emphasized that so-called "posterior" ischemia or necrosis is in reality an injury to the inferior surface of the heart.

Papp and Smith[5] have devoted special attention to the clinical course of "slight coronary attacks." They called attention to the infrequency of shock and cardiac failure, the minimal blood pressure changes, the lack of clinical and laboratory evidence of "myocardial necrosis" and the uniformity of uncomplicated recovery in thirty-five patients. In twenty-eight instances "complete restoration to normal or far-reaching electrocardiographic recovery" occurred. Recovery took place in about two months in five patients, and in from four to sixteen months in twenty-three patients. Most of the cases described by Papp and Smith[5] began spontaneously without the precipitating factors noted by Master and Jaffe.[1] However, Master too pointed out the good prognosis with acute coronary insufficiency; a 9 per cent mortality in a three to twenty year follow-up compared with a 28 per cent mortality in acute myocardial infarction. Master stated that in 57 per cent of patients with coronary insufficiency the "heart and electrocardiogram returned to normal"; only 16 per cent of those with myocardial infarction returned to normal.

In this series of twenty-four patients with acute coronary insufficiency, 75 per cent showed involvement of the anterior surface of the heart; only 41 per cent of the twenty-seven patients with acute myocardial infarction had anterior lesions. The clinical course of acute coronary insufficiency in general paralleled that of acute myocardial infarction. Prolonged pain, leukocytosis, elevation of the sedimentation rate, and two to four weeks of hospitalization occurred in both illnesses. Acute coronary insufficiency was on the whole a less severe illness, as shown by the absence of shock, infrequency of failure and lack of fatality during the acute attack.

Acute myocardial infarction has been subjected to vectorcardiographic study by Grishman and Scherlis[17] who analyzed abnormalities of the QRS loop in patients who had recovered from acute myocardial infarction, but no studies were done during the course of their illness. The conventional 12-lead electrocardiogram does not lend itself to quantitative analysis easily. In direct spatial vectorcardiography T-wave changes are most difficult to evaluate; it was for these reasons that the methods of vector electrocardiography of Grant and Estes[7] and Simonson[8] were adopted.

In the analysis of acute myocardial infarction by vector electrocardiography, the QRS vector followed in general the pathway outlined by Grishman and Scherlis[17] and pointed away from the infarcted area. The degree of vector shift was influenced by the following factors: (1) the QRS complex was treated as a whole and the initial component was not isolated as a separate entity. For example, in anterior myocardial infarction the presence of a Q wave in Lead I of 2 to 3 mm. in depth would have little effect on the vertical angle of QRS. Likewise in acute posterior myocardial infarction, particularly in a heart horizontal in position, the loss of a small R wave in Lead III would not alter the vertical angle appreciably. (2) Unexplained shifts in axis and in voltage, particularly when the voltage was low, occasionally resulted in significant shifts of the QRS vector apart from Q wave changes. These usually occurred during the acute phase of the attack and may have been due to transient cardiac failure, with or without pericardial effusion. (3) Technical errors in positioning of the precordial electrodes may produce shifts in the horizontal angle of QRS. In this series these errors were corrected when there were sufficient numbers of electrocardiograms. (4) In some cases the extent of the QRS vector shift was not apparent because there was no normal electrocardiogram available for comparison.

In marked contrast to the minimal degree of shift of the QRS vector in acute myocardial infarction, the shift of the T vector was extreme. The general pathway of the T vector was away from the area injured, similar to the pathway of the QRS vector. The T vector shifted posteriorly in infarctions involving the anterior surface of the heart, and upward in those involving the posterior surface. The sequential shifts during the course of an acute infarction were registered in the apparent rotation of the T vector, which appeared to follow a circular pathway, gradually turning further and further away from the infarcted area. The greater the number of leads with abnormal T-wave inversion, the greater was the vector shift, usually. If it is presumed that the extent of the area of infarction can be determined roughly by the number of precordial leads showing T-wave inversion, then a relationship should exist between the size of the infarction and the degree of the T vector shift. It was shown that in a small number of cases with anteroseptal infarction, those with the greatest degree of vector shift were the most seriously ill. Although the reasoning is indirect and the number of cases in this series small, the data appears to be worth reporting. It is not an uncommon clinical experience to judge the size of the infarction on the basis of either a wide distribution of Q waves or a wide-spread T-wave inversion. No report in the literature could be found, either from a clinical or pathologic point of view, which attempted to make such a correlation. It should be emphasized again that such a correlation may only be attempted in anterior myocardial infarction, since only in this situation may a number of semidirect leads "explore" any reasonably large myocardial surface. As seen in Table III, there was no correlation between the clinical course of a posterior infarction and the degree of the T-vector shift in the vertical plane.

In acute coronary insufficiency, the T-wave vector has presented the following differences from the T-wave vector in myocardial infarction: (1) The shift

is considerably less marked in acute coronary insufficiency. (2) The maximum shift of the T vector is usually seen on the third or fourth day, rather than during the second week. (3) Reciprocal S-T segment shifts are less frequent. (4) There is a more frequent involvement of the anterior portion of the heart.

Quantitative differences were present during the recovery phase in acute coronary insufficiency and acute myocardial infarction. In four of the twenty-seven patients with acute myocardial infarction, the electrocardiogram became completely normal. This was the case in seven of the twenty-four patients with acute coronary insufficiency. These figures agree fairly closely with those of Master.[1] It was also of interest to observe the time at which the electrocardiogram ceased to change. This was on the average much earlier (59 days) in acute coronary insufficiency than in acute myocardial infarction (137 days).

SUMMARY

1. In twenty-seven patients with acute coronary insufficiency and in twenty-four patients with acute myocardial infarction, electrocardiograms and mean spatial vectors of QRS and T have been described and compared.

2. Acute coronary insufficiency is a common clinical entity, at least half as common as acute transmural myocardial infarction.

3. The diagnosis of acute coronary insufficiency may be made with reasonable accuracy and implies an area of subendocardial necrosis which is anterior in location three times as frequently as posterior.

4. The mean spatial vector of QRS, being a composite figure, shows little change in myocardial infarction, and, of course, in coronary insufficiency.

5. The mean spatial T-vector shift is greater in acute myocardial infarction than in acute coronary insufficiency. The maximum shift occurs earlier, on the third day in acute coronary insufficiency, and considerably later in myocardial infarction.

6. In acute myocardial infarction, anterior in location, there is a close correlation between the degree of shift of the mean spatial T vector and the severity of the illness. Thus in this situation the degree of shift of the T vector appears to be a measure of the extent of myocardial injury.

7. Complete electrocardiographic recovery occurs more frequently in acute coronary insufficiency; also the attainment of a stable electrocardiogram occurs earlier than in acute myocardial infarction.

8. Vector-electrocardiography is of real value in acute coronary insufficiency and in acute myocardial infarction; it is a semiquantitative yardstick for the more detailed appraisal of the degree of myocardial injury and the amount of recovery.

SUMMARIO IN INTERLINGUA

In 27 patientes con acute insufficientia coronari e in 24 patientes con acute infarcimento myocardiac, electrocardiogrammas routinari esseva usate pro derivar vectores spatial median de QRS e de T. In acute insufficientia coronari

(que ha un frequentia de circa un medietate de illo de acute infarcimento myocardiac), le diagnose pote facer se con adequate exactitude. Il ha in iste casos un area de necrosis subendocardiac, e le location de illo es tres vices plus frequentemente anterior que posterior. Le vector de QRS monstra pauc cambiamento in infarcimento e in insufficientia. In infarcimento, comparate con insufficientia, le displaciamento de T in le vector es plus grande, le maximo del displaciamento occurre plus tarde, le retorno al norma es minus complete e minus frequente, e un traciamento stabile superveni a un data plus retardate. In acute infarcimento myocardiac anterior il existe un nette correlation inter le grado de displaciamento del vector de T e le severitate del morbo. In iste sito le grado del displaciamento del vector de T pareva representar un mesura del extension del lesion myocardiac.

The authors wish to express appreciation to Pacific Mutual Life Insurance Company and to the Kalash Vitamin Corporation for their interest and support in this study; and to Dr. Robert Oblath for valuable editorial assistance.

REFERENCES

1. Master, A. M., and Jaffe, H. L.: Complete Functional Recovery After Coronary Occlusion and Insufficiency, J.A.M.A. **147**:1721, 1951.
2. Freedberg, A. S., Blumgart, H. L., Zoll, P. M., and Schlesinger, M. J.: Coronary Failure, the Clinical Syndrome of Cardiac Pain Intermediate Between Angina Pectoris and Acute Myocardial Infarction, J.A.M.A. **138**:107, 1948.
3. Levine, H. D., and Ford, R. V.: Subendocardial Infarction: A Report of Six Cases and a Critical Survey of the Literature, Circulation **1**:246, 1950.
4. Yu, P. N. G., and Stewart, J. M.: Subendocardial Myocardial Infarction With Special Reference to the Electrocardiographic Changes, AM. HEART J. **39**:862, 1950.
5. Papp, C., and Smith, K. S.: Electrocardiographic Assessment of Posterior Cardiac Infarction, AM. HEART J. **44**:696, 1952.
6. Miller, R. D., Burchell, H. B., and Edwards, J. E.: Myocardial Infarction With and Without Acute Coronary Occlusion, Arch. Int. Med. **88**:597, 1951.
7. Grant, R. P., and Estes, E. H., Jr.: Spatial Vector Electrocardiography, Philadelphia, 1951, The Blakiston Company.
8. Simonson, E.: A Spatial Vector Analyzer for the Conventional Electrocardiogram, Circulation **7**:403, 1953.
9. Simonson, E., and Keys, A.: The Spatial QRS and T Vector in 178 Normal Middle-aged Men. Body Weight, Height, Relationship of QRS and T, and Preliminary Standards, Circulation **9**:105, 1954.
10. Milnor, W. R., Talbot, S. A., and Newman, E. V.: A Study of the Relationship Between Unipolar Leads and Spatial Vectorcardiograms, Using the Panoramic Vectorcardiograph, Circulation **7**:545, 1953.
11. Prinzmetal, M., Shaw, C. M., Jr., Maxwell, M. H., Flamm, E. J., Goldman, A., Kimura, N., Rakita, L., Borduas, J., Rothman, S., and Kennamer, R.: Studies on the Mechanism of Ventricular Activity VI. The Depolarization Complex in Pure Subendocardial Infarction; the Role of the Subendocardial Region in the Normal Electrocardiogram, Am. J. Med. **16**:469, 1954.
12. Pardee, H. E. B., and Goldenberg, M.: Electrocardiographic Features of Myocardial Infarction as Affected by Involvement of the Septum and by Complete and Incomplete Transmural Involvement, AM. HEART J. **30**:367, 1945.
13. Myers, G. B., Klein, H. A., and Stofer, B. E.: I. Correlation of Electrocardiographic and Pathologic Findings in Anteroseptal Infarction, AM. HEART J. **36**:535, 1948.
14. Myers, G. B., Klein, H. A., and Hiratzka, T.: II. Correlation of Electrocardiographic and Pathologic Findings in Large Anterolateral Infarcts, AM. HEART J. **36**:838, 1948.
15. Myers, G. B., Sears, C. H., and Hiratzka, T.: Correlation of Electrocardiographic and Pathologic Findings in Ring-Like Subendocardial Infarction of the Left Ventricle, Am. J. M. Sc. **222**:417, 1951.
16. Lepeschkin, E.: Modern Electrocardiography, The P-Q-R-S-T-U-Complex, Baltimore, 1951, The Williams and Wilkins Company, pp. 805-807.
17. Grishman, A., and Scherlis, L.: Spatial Vectorcardiography, Philadelphia, 1952, W. B. Saunders Company.

SPECTRAL PHONOCARDIOGRAPHIC DEMONSTRATIONS OF SELECTED VARIETIES OF CARDIOVASCULAR SOUNDS

VICTOR A. MCKUSICK, M.D., EDMUND W. KLINE, M.D., AND GEORGE N. WEBB, M.S.

BALTIMORE, MD.

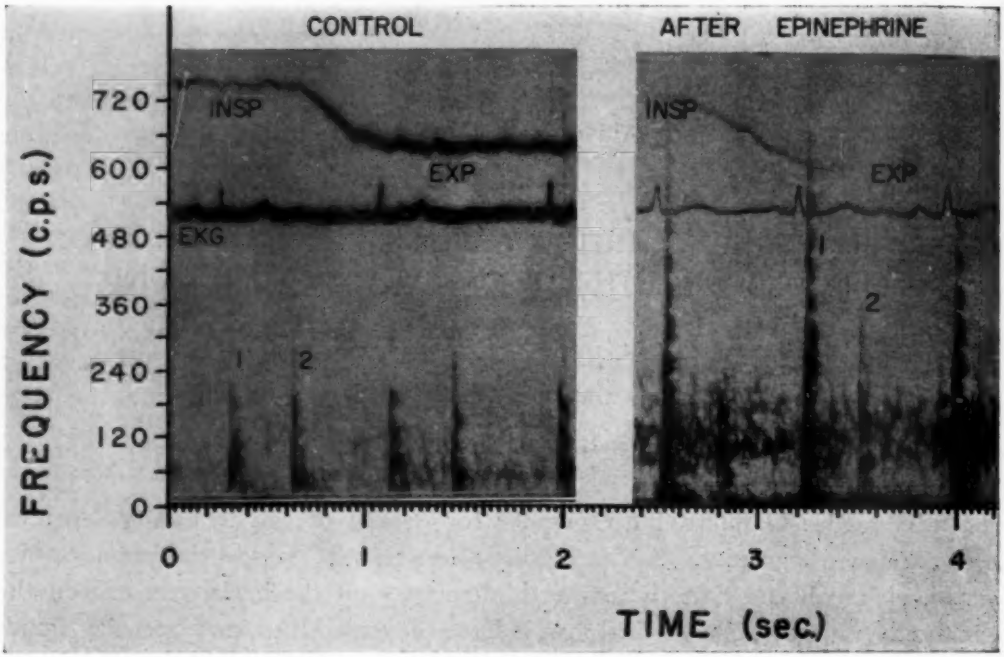
THE reader is referred elsewhere[1-3] for details of the technique, spectral phonocardiography. Suffice it to say here that in the spectral phonocardiogram, although the time dimension is displayed on the horizontal axis in the customary manner, the vertical axis is frequency spectrum, not intensity (loudness). Intensity is represented by degree of blackness in any given portion of the record.

The purpose of this communication is to demonstrate further certain varieties of cardiovascular sound and to discuss some technical aspects of spectral phonocardiographic design. Recordings of heart sounds were made on magnetic tape using a condenser-type microphone.[2] Electrocardiogram and respiratory tracings were simultaneously recorded on the tape by means of frequency modulated carriers.[2,3] A more valid recording was obtained, with less risk of introduction of physiologic artifact as a result of partial Müller or Valsalva experiment, by permitting quiet respiration during the recording. Since artifacts such as breath sounds are easily identified as such in the spectral phonocardiogram, respiration does not interfere with the analyses. The actual displays were made using a Bell sound spectrograph (Kay Vibralyzer), modified for phonocardiography.[3] All displays presented here were made on direct-writing, electro-sensitive paper.

From the Department of Medicine, Johns Hopkins University School of Medicine and Johns Hopkins Hospital, Baltimore 5, Md.

Work supported in part by a grant-in-aid from the National Heart Institute and in part by a contract between Johns Hopkins University and the U. S. Air Force (Office of Scientific Research, Air Research and Development Command).

Received for publication Jan. 22, 1955.



A. *B.*

Fig. 1.—*Effect of Epinephrine on Normal Heart Sounds.* Demonstrated in *A* are the heart sounds recorded at the lower left sternal border in a normal subject. In *B* is a recording from the same area made under identical conditions of amplification five minutes after the administration of 1.0 c.c. of epinephrine, 1:1,000 subcutaneously. The second heart sound is little changed. (Systemic blood pressure was 110/70 mm. Hg during the control recording and 114/64 mm. Hg after epinephrine.) The striking change in the first sound consists of increase in peak frequency (frequency span), appearance of more conspicuous harmonics, and increase in over-all loudness as indicated by blackness. The first two features account for the impression of snappiness which the first sound after epinephrine conveys to the ear.

The accentuation of the first sound is probably closely related to the subjective palpitation which accompanies epinephrine administration. Increase in the *velocity* of valve closure is probably principally responsible for the accentuation. No great increase in ventricular pressure would be anticipated on the basis of studies of the systemic and pulmonary arterial pressure. An abbreviation of isometric contraction with accelerated rise in intraventricular pressure has been demonstrated[4] after administration of epinephrine. As is demonstrated in Fig. 1,*B*, higher frequencies are produced, and it is largely the contributions of these to total intensity which are responsible for the over-all intensification. As stated by Lamb,[5] ". . . according to a general principle . . . the higher harmonics are excited in greater relative intensity the more abrupt the character of the originating disturbance."

Consideration of the relation of the duration of the isometric contraction phase to the intensity of the first sound makes it apparent that no direct relationship between "cardiac vibrational intensity" and cardiac output is possible.[6] Prolongation of isometric contraction is probably responsible, in large degree, for the dull or muffled heart sounds of myocardial disease. In this case the sounds are of low frequency and the low total intensity is, to a considerable extent, the result not of attenuation of these low-frequency components, but of absence of higher frequency contributions. The dull first heart sound in myocardial disease is largely due to slower, less snappy closure of the A-V valves than normal.

Strictly speaking, it is not duration of isometric contraction per se which is operating to change the first sound in these instances since, by definition, the A-V valves are already closed during this period. However, there is in general a direct relationship between the velocity with which they are closed and the duration of isometric contraction.

(Excessive background noise appeared in the recording after administration of epinephrine. The amplification during the stages of recording and analyzing was identical in the two cases. Several explanations for the increased background noise in the second recording are possible: (1) increase in ambient (room) noise, (2) muscle noise from the tension engendered by the drug, (3) vascular noise from circulatory changes.)

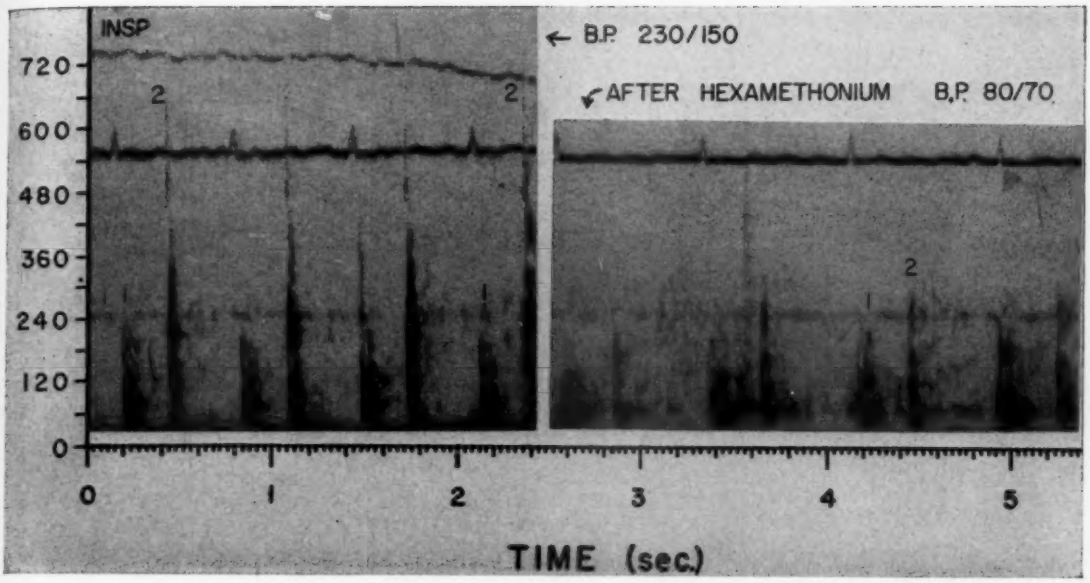


Fig. 2.—*Heart Sounds Before and After Administration of Hexamethonium to a Hypertensive Patient.* In this pair of tracings from the left lower sternal border, variations in blood pressure were accompanied by little change in the first heart sound which in each instance is slightly split into mitral and tricuspid components. At the hypertensive level the second sound is louder (blacker) and has a greater frequency span. The variable involved here is *force* of closure. Velocity of closure, an important factor in the accentuation of the first sound (S_1) in Fig. 1, is intimately related to force of closure. Certain it is that aortic valve closure is more rapid at elevated levels of diastolic pressure.

Electrical interference at 240 cycles is demonstrated.

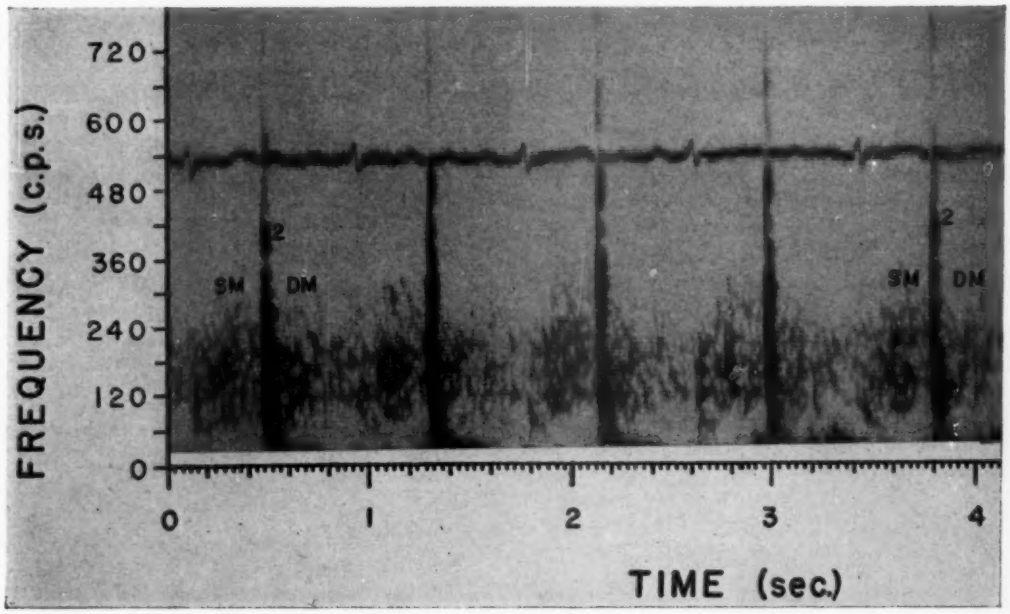


Fig. 3.—*Rheumatic Aortic Valvular Disease in Normotensive 20-Year-Old Patient.* There is a systolic murmur produced probably by a moderate degree of aortic stenosis. This murmur has a peak of intensity and frequency in mid-systole. (See Figs. 4 and 5 for demonstrations of the more fully developed pattern.) The second sound is followed immediately by a decrescendo diastolic murmur. The pulse pressure in this patient is not widened and the patient is in general asymptomatic. The greatly accentuated second sound (S_2) is noteworthy. There is a wide-frequency span and intensification of the sound throughout the normal frequency range. The intensification of S_2 in this instance is due to *fibrosis* of the valve. Such a fibrosed valve would be expected to produce a noisier closure.

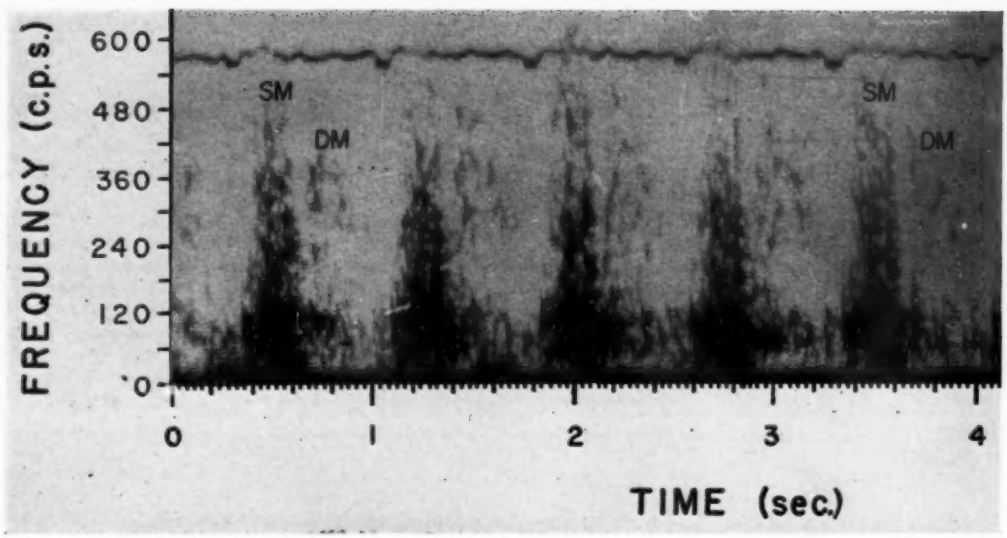


Fig. 4.—*Rheumatic Aortic Stenosis and Regurgitation.* The typical ejection stenosis murmur has a peak of both intensity and frequency in mid-systole. The resulting pattern suggests a Christmas tree. A particularly interesting feature of this case is the high pitch of the relatively faint diastolic murmur. The patient also has right bundle branch block. Lead II of the electrocardiogram is displayed.

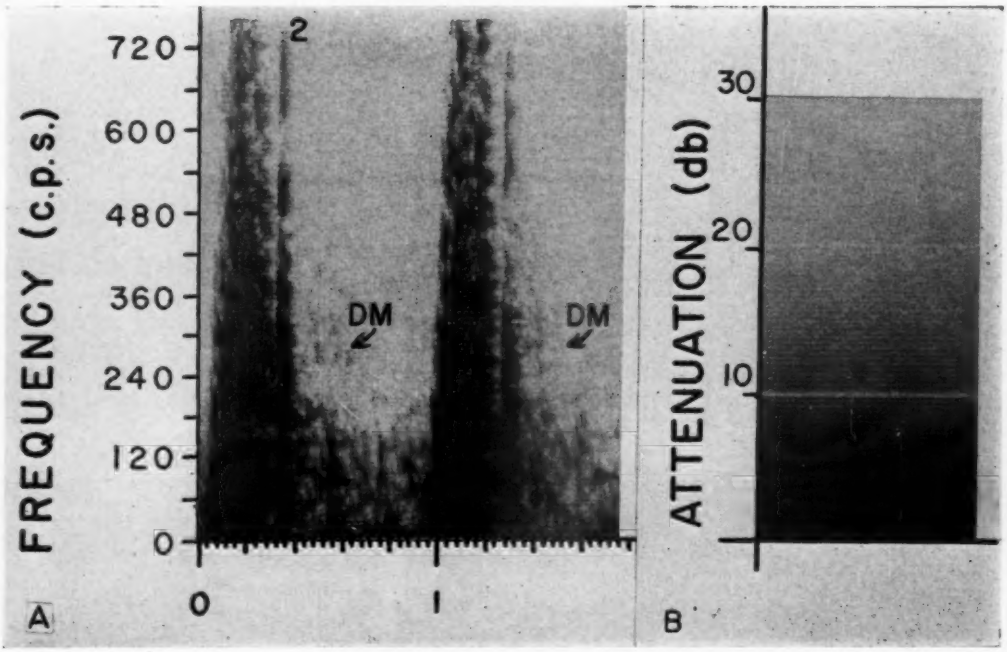


Fig. 5.—*Rheumatic Aortic Stenosis and Regurgitation.* Again the typical Christmas tree pattern of the murmur of aortic stenosis is displayed, as well as the doubly decrescendo pattern of the very faint diastolic murmur. In the display of the wide dynamic range of cardiovascular sound, spectral phonocardiography improves greatly on the performance of conventional oscillographic phonocardiography. In the example given here (*A*) the systolic murmur is estimated to be about 60 db more intense than the diastolic murmur, a 1,000 fold difference. There is no way by oscillography that these two murmurs can be simultaneously displayed in their true proportions. In order to record the diastolic murmur with a maximum height of 3.0 mm., the systolic murmur would have a height of approximately ten feet. Using pass-band filters will not solve the problem since the tremendous dynamic range is present at the frequency level where the diastolic murmur is most intense, about 280 c.p.s., in this case. In its ability to encompass the very large dynamic range of sound, spectral phonocardiography resembles the ear. This point is also demonstrated, although somewhat less dramatically by the systolic and diastolic murmurs seen in Fig. 4. Technical developments in spectral phonocardiography must take this dynamic range into account. In the tape recording, maximum dynamic characteristics must be provided and the display medium must permit widest possible density grading from black to white. Photographic displays have a considerable advantage over the direct-written records shown here. The display on electro-sensitive paper by our present technique provides a dynamic range of about 15 db (*B*). This last deficiency accounts for the homogeneous blackness of the lower frequency range of the systolic murmur in *A*. The harmonic pattern of this portion of the murmur is completely obscured.

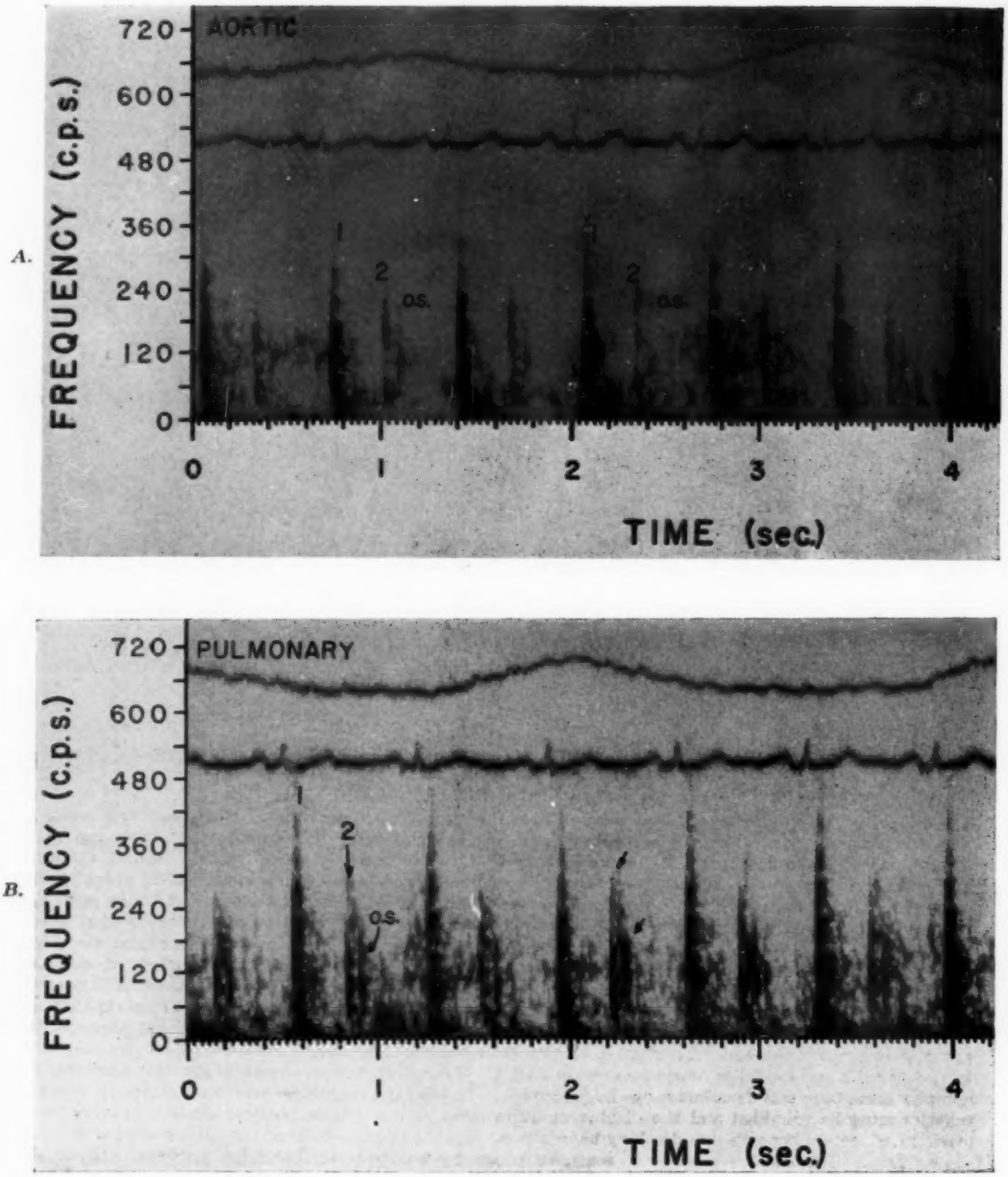


Fig. 6.—*Typical Rheumatic Mitral Stenosis.** In the aortic area the heart sounds are characteristically quiet. An accentuated second sound would suggest rheumatic fibrosis of this valve (Fig. 3). The first sound is more striking than usual; its timing relative to the QRS (i.e., its delay) indicates that it is the mitral closure sound heard in the aortic area with unusual clarity because of its accentuation. No splitting of A_2 is demonstrated; only aortic closure is represented. The opening snap (O.S.) is well demonstrated in the aortic as in other areas. In the pulmonary area, on the other hand, the second sound is split, especially during inspiration (see the upper arrow in the case of the fourth S_2,*B*). The simultaneous demonstration of a split second sound and the opening snap leaves little doubt of the identity of the separate sounds. There is probably little pulmonary hypertension in this case. The split second sound and opening snap are similarly well demonstrated at the lower left sternal border. At the apex the mitral closure sound is accentuated and delayed. The second sound is unitary and, as is normally the case, is the result of aortic valve closure. The diastolic rumble begins immediately with the opening snap. It is first decrescendo, then crescendo in presystole.

*In the tracing of respiratory phase at the top of each recording, inspiratory movement is upward and expiratory movement downward.

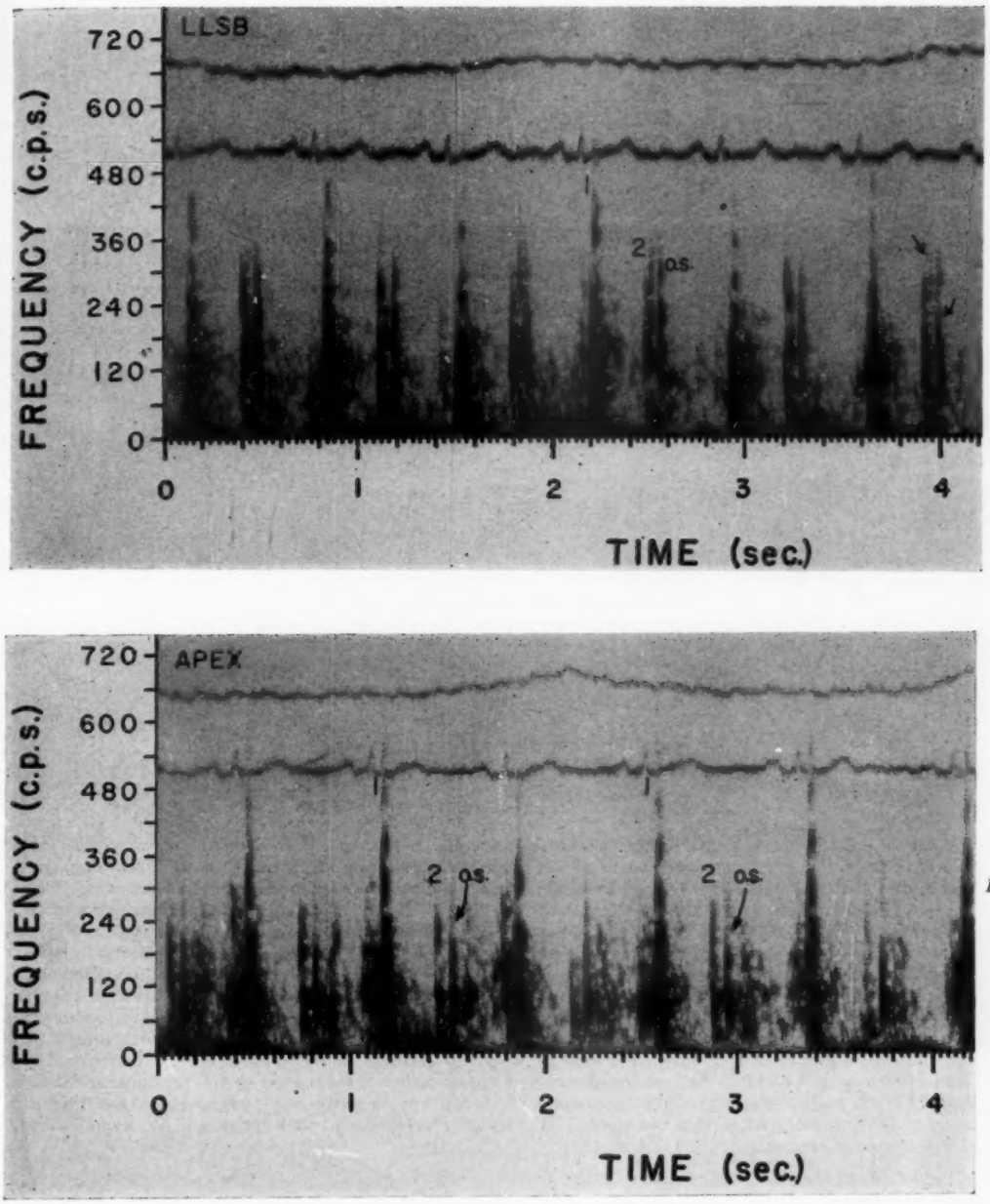


Fig. 6, *C* and *D*.—*(For legend see opposite page.)*

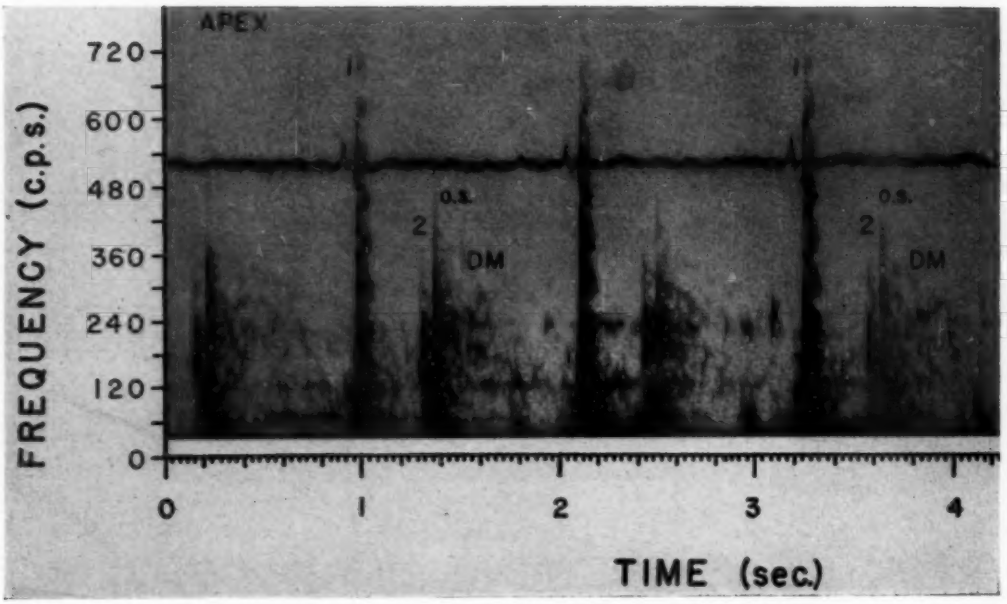


Fig. 7.—*Rheumatic Mitral Stenosis With Unusually High-pitched Diagnostic Murmur.* In this recording from the apex the appearance of the characteristic snapping mitral first sound is displayed. It is louder than normal, has a greater frequency span, and has a conspicuous harmonic pattern. This, the mitral closure sound, is delayed relative to the QRS. The mechanism of the accentuation of the mitral closure sound of mitral stenosis is probably in the main the same as that represented in Fig. 3: fibrosis of the valve structure. S_2 is followed by a striking opening snap. The snapping quality of the opening snap is usually clearly enough demonstrated in the spectral phonocardiogram, being characterized usually by more uniform, homogeneous distribution of intensity on the frequency scale than is the case with valve closure sounds. The opening snap is followed immediately by a diastolic murmur of appreciably higher pitch than is usually found in mitral stenosis (compare with the "rumble" in Fig. 6). All features of this case were typical of mitral stenosis of moderately severe degree. That this murmur in fact had its origin at the obstructed mitral orifice is supported by its disappearance after mitral valvulotomy. In spite of the presence of sinus rhythm no presystolic component of the diastolic murmur is demonstrated in this recording. Electrical interference at 120 cycles and, to some extent, at 240 cycles is present.

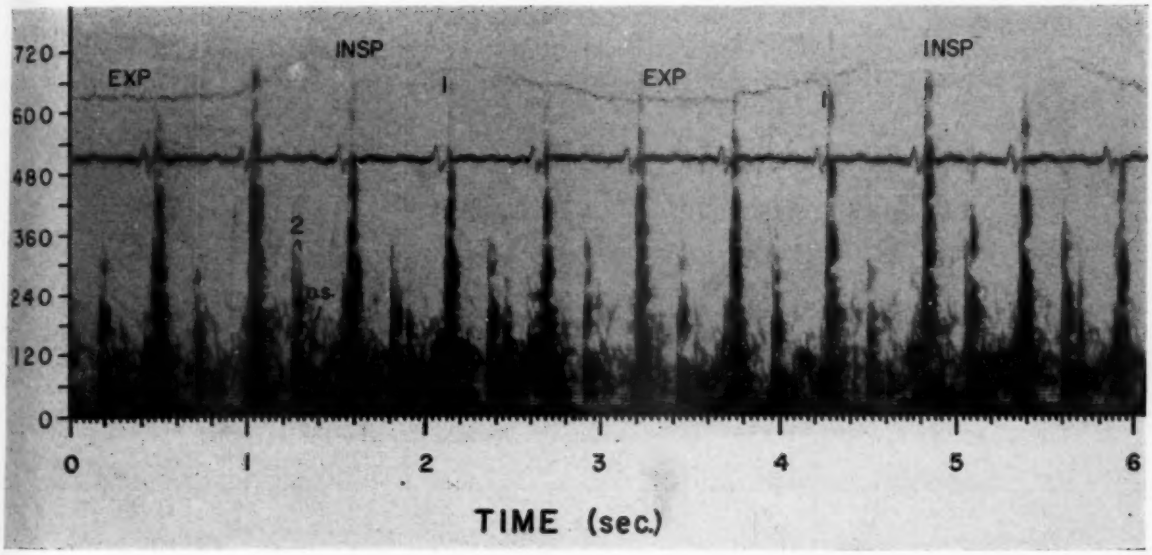
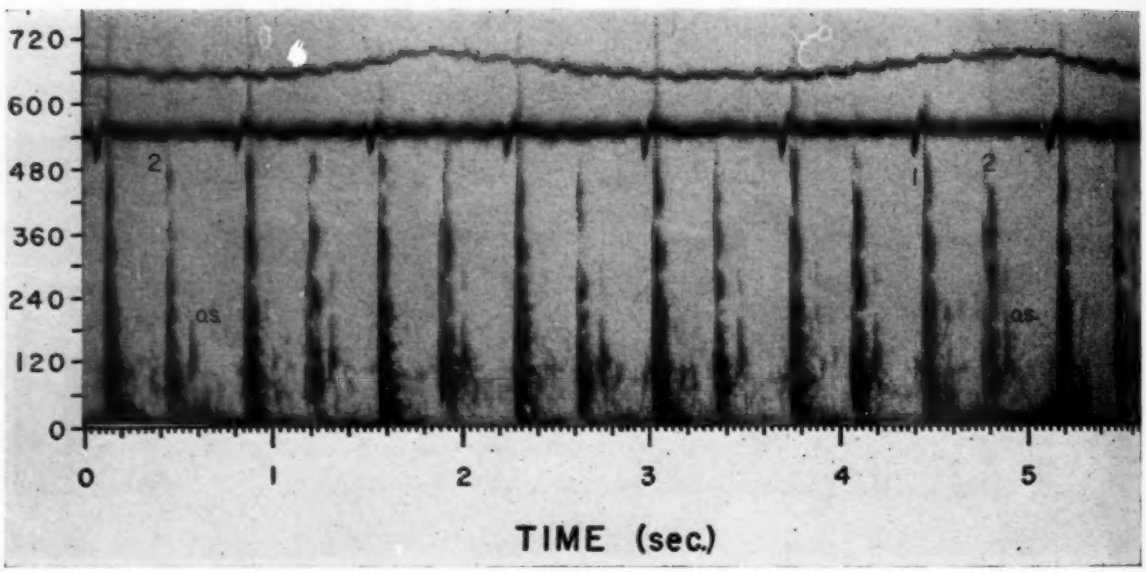


Fig. 8.—*Changes in the Diastolic Murmur of Mitral Stenosis With Respiration.* With inspiration the second sound becomes split, and it is then the second component (pulmonary valve closure) which dominates. The fact that pulmonary valve closure is so well heard at the apex bespeaks considerable pulmonary hypertension (contrast Figs. 6 and 7). The diastolic rumble is intensified early in expiration. Intensification of the diastolic murmur of tricuspid stenosis is likely to occur in inspiration.



A.

Fig. 9.—*The Influence of Atrioventricular Pressure Gradient on S_2-O.S. Interval.* (See footnote for Fig. 6.) The recording in *A* is from the pulmonary area of a patient with severe arterial hypertension and a mild degree of mitral stenosis. The accentuation of the first heart sound has two bases in this case: increased force of closure and fibrosis of the mitral valve. The second sound becomes split with inspiration. In spite of the systemic hypertension the pulmonary closure sound predominates. Of particular note is the unusually great S_2-O.S. interval, measuring 0.14 sec. from beginning of S_2 to beginning of opening snap, in most cycles. In general, lesser grades of mitral stenosis with less elevation of left atrial pressure are accompanied by longer S_2-O.S. interval.[7] Other clinical evidence indicates only a low grade of mitral obstruction in this case. A second factor in the S_2-O.S. prolongation in this particular case is the systemic hypertension. The patient's blood pressure, 230/140 mm. Hg at the time of this recording, suggests that aortic valve closure might occur perhaps at 180 mm. Hg and that an appreciably longer time will be required for intraventricular pressure to fall to the level of intra-atrial pressure, at which time the opening snap will occur. These considerations are graphically presented in *B*.

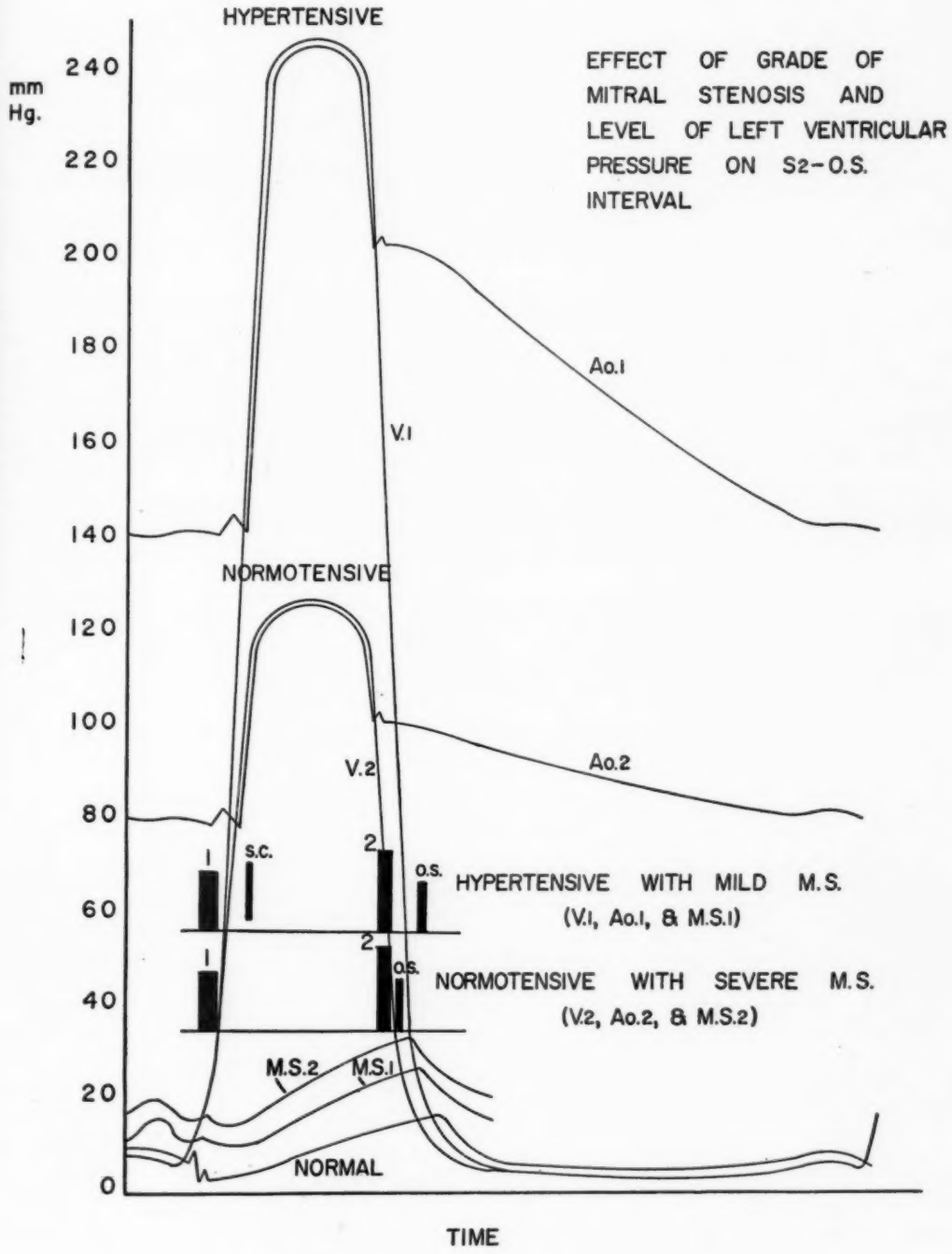


Fig. 9 *B.*—*(For legend see opposite page.)*

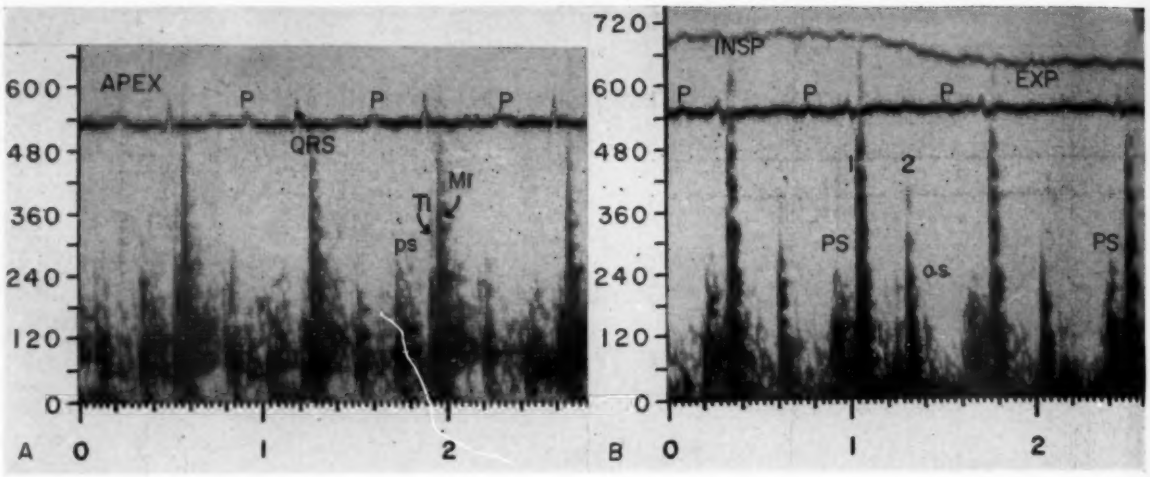


Fig. 10.—*Rheumatic Mitral Stenosis With Prolonged Atrioventricular Conduction.* Fundamentally the presystolic murmur of mitral stenosis is the same as the systolic murmur of aortic or pulmonary stenosis. All are "ejection stenosis" murmurs. In the case of the presystolic murmur of mitral stenosis, the typical Christmas tree pattern is cut short by the snapping first sound when the atrioventricular interval is of normal duration. When the atrioventricular interval is prolonged, as in these cases, the typical pattern becomes evident. In *A* the first sound is split. Tricuspid closure occurs in its normal relation to the QRS. Mitral valve closure, which normally occurs slightly earlier than, or coincident with tricuspid closure, is delayed and accentuated. Usually in mitral stenosis the presystolic murmur obscures the tricuspid closure sound. In fact, the tricuspid closure sound often contributes to the presystolic crescendo. In *B* the same Christmas tree pattern of the presystolic murmur is demonstrated because of P-R prolongation. This recording was made after mitral valvulotomy. A faint opening snap persists.

The persistence of the snapping character of the mitral closure sound in the presence of the prolonged P-R suggests that a widespread position of the mitral orifice as a result of elevated left atrial pressure is not the main factor responsible for the snapping M_1 of mitral stenosis.

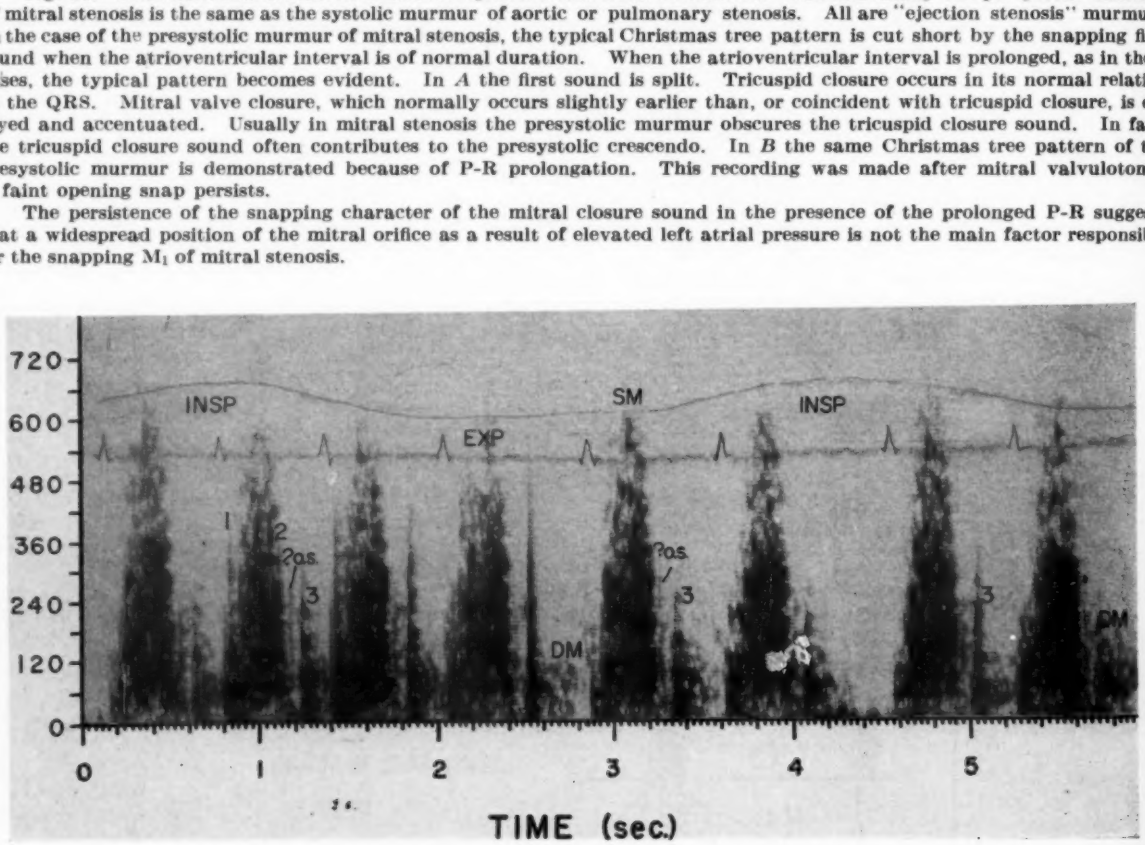


Fig. 11.—*Rheumatic Mitral Regurgitation.* In this case the systolic murmur begins with the second component of the first sound (mitral closure). The first sound is, in general, dull. In this case, the systolic murmur, although holosystolic, is crescendo rather than decrescendo (compare Fig. 12,*A*). A striking third heart sound gallop is present. This shows variation with respiratory phase being more conspicuous during expiration. It is followed by a short, low-pitched murmur ("rumble"). In the gap between the second snap and the third sound there is a faint sound. That this is an opening snap and not the second part of a split second sound is suggested by the fact that its relationship to the second sound shows no variation with respiration. Obviously the presence of an opening snap, especially in records as refined as this for demonstrating it, is not evidence that significant mitral stenosis is present. On the other hand its absence (see the case illustrated in Fig. 12,*A*) is strong evidence against the existence of significant mitral stenosis. Elsewhere[3] we have illustrated the cycle-to-cycle variation in QRS-S_1 delay and in S_2-O.S. interval which occurs in patients with pure mitral stenosis and atrial fibrillation. Evidence has been presented by Kuo and Schnabel[8] that this variability (related to the length of the previous diastolic period) does not occur when significant mitral regurgitation (or aortic regurgitation) is present. The present recording is consistent with their findings since the intervals in question are of fixed duration. (In predominant mitral stenosis[9] the QRS-S_1 delay increases and the S_2-O.S. interval shortens as diastole shortens. With longer diastolic periods, pressure in the left atrium reaches a lower level, and vice versa. The higher the intra-atrial pressure is, the later mitral closure occurs, and the earlier the opening snap occurs.)

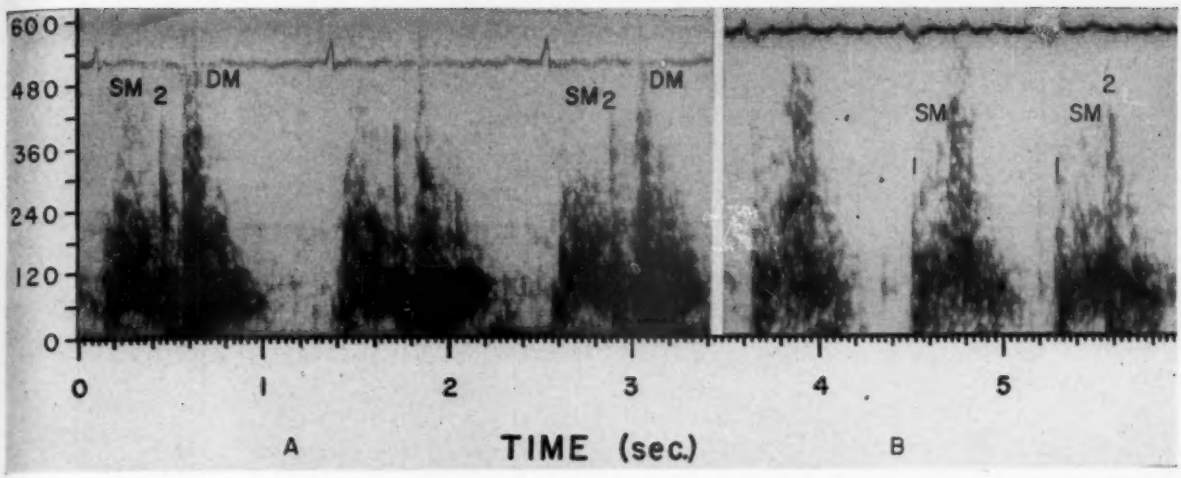


Fig. 12.—*Rheumatic Mitral Regurgitation.* The recording in *A* was made from a patient who was explored with the intent of performing mitral valvulotomy. Pronounced mitral regurgitation and very little mitral obstruction were discovered. At the apex the first sound is muffled. Possibly two components can be faintly discerned. A decrescendo systolic murmur begins immediately with the second component which is probably a delayed mitral closure sound. The second sound at the apex, which probably has its origin largely in closure of the aortic valve is followed by a gap before the beginning of the diastolic rumble. The diastolic rumble begins abruptly with a third sound gallop. Note that no opening snap is demonstrated. That an opening snap does not initiate the rumble is supported by the fact that the interval between the second sound and the beginning of the rumble is longer than usual S_2-O.S. interval. The protodiastolic gallop is exceedingly loud, louder in fact than the "normal" heart sounds.

Among the conditions which can simulate mitral stenosis should be listed mitral regurgitation. Dilatation of the ventricle and increased blood flow across the mitral orifice because of regurgitation in previous cycles are the responsible factors in this relative mitral stenosis. In this instance *B*, the systolic murmur, is crescendo in type. Right bundle branch block is present. Mitral closure may be delayed, but the delay of tricuspid closure as a result of the bundle branch block may tend to result in superimposition of the two components. (Splitting of the second sound is barely discernible in some cycles.) The murmur continues directly on into early diastole. It is not unexpected that in some anatomic varieties of regurgitant mitral valves regurgitation into the left atrium should continue after closure of the aortic valve and until the time that pressure in the left ventricle has fallen below that in the left atrium. Then a reversal of flow will occur. The net result is that a continuous to-and-fro murmur occurs.

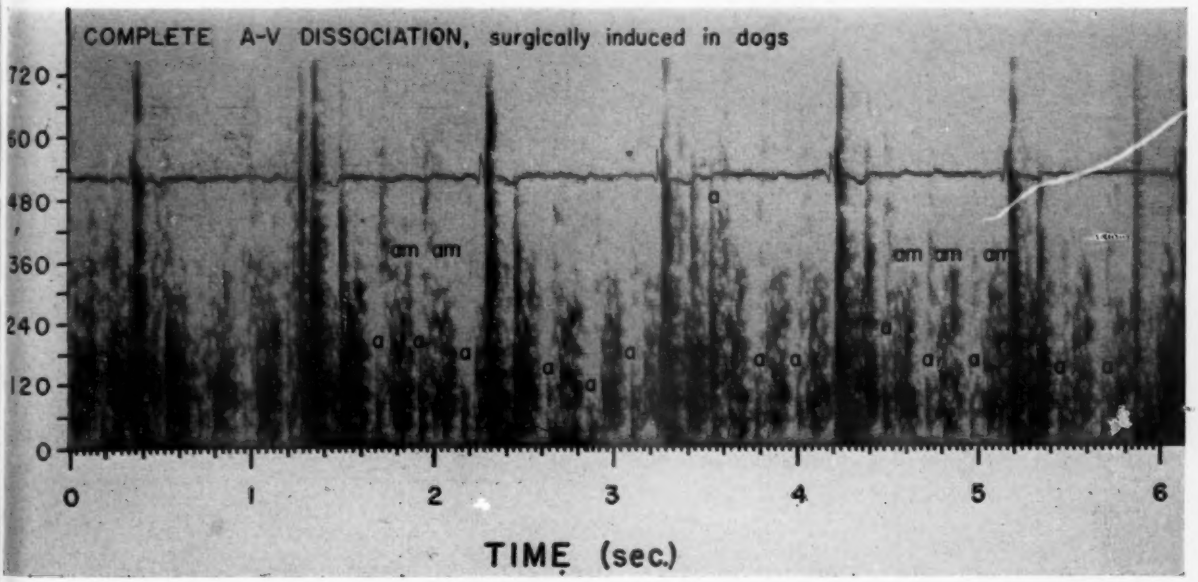


Fig. 13.—*Surgically-induced Complete Heart Block in the Dog.* Third degree heart block was produced by Dr. T. E. Starzl by the method he and his collaborators have described elsewhere. A circumscribed sound ("*a*") occurs with tensing of the atria and is followed by a murmur ("*am*") related presumably to the passage of blood into the ventricle. The occurrence of this phenomenon, an atrial sound followed by an atrial murmur, has been described in elderly patients with complete heart block.[10] Variation in the intensity and frequency span of the first sound is demonstrated. This record is too short to demonstrate convincingly that the louder sounds occur with the shorter P-R intervals but such did appear to be the case. This recording was made one month after operation for creation of heart block. Although it seems unlikely to the writers, a pericardial origin of the sounds following each atrial sound cannot be unequivocally excluded.

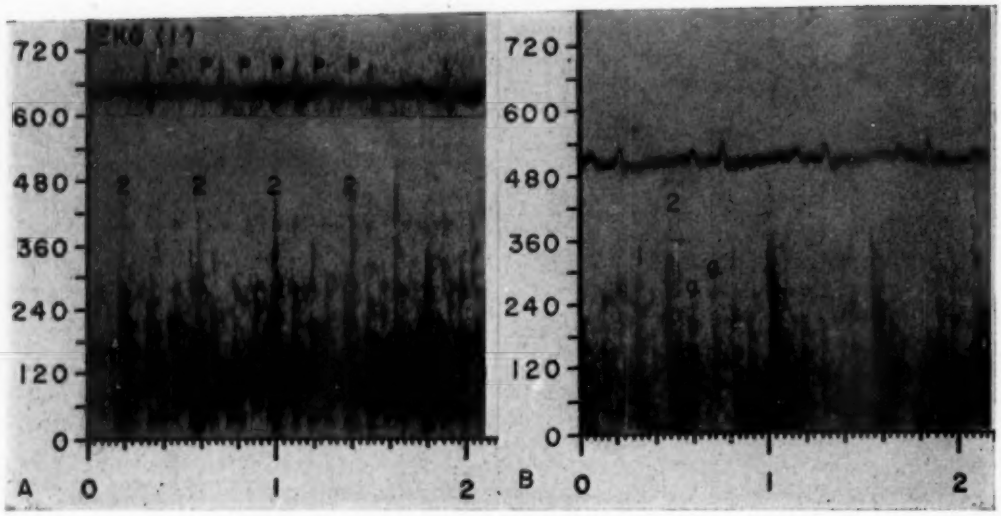


Fig. 14.—*Quadruple Rhythm.* In the example presented in *A* (aortic area) the patient had paroxysmal atrial tachycardia with 2:1 atrioventricular block. Each atrial contraction is accompanied by a sound: one in systole, one in diastole. The second heart sound is slightly split in some instances. The occurrence of an atrial sound in ventricular systole, when the atrioventricular valves are certainly closed, is evidence that tensing of the atrium and not movement of blood into the ventricle is primarily responsible for its production. In the electrocardiogram shown here the presence of two negative P waves between each two QRS's is not clearly demonstrated but was clear from conventional electrocardiograms.

In the recording in *B*, also from the aortic area, the quadruple rhythm results from the presence of both protodiastolic and presystolic gallop (*g*) sounds. The patient has cor pulmonale due to multiple pulmonary emboli. The second sound is accentuated and is followed by a short diastolic murmur of presumed pulmonary origin. "P pulmonale" is demonstrated by the electrocardiogram. An early systolic click of dilated pulmonary artery makes this a quintuple rhythm in some cycles.

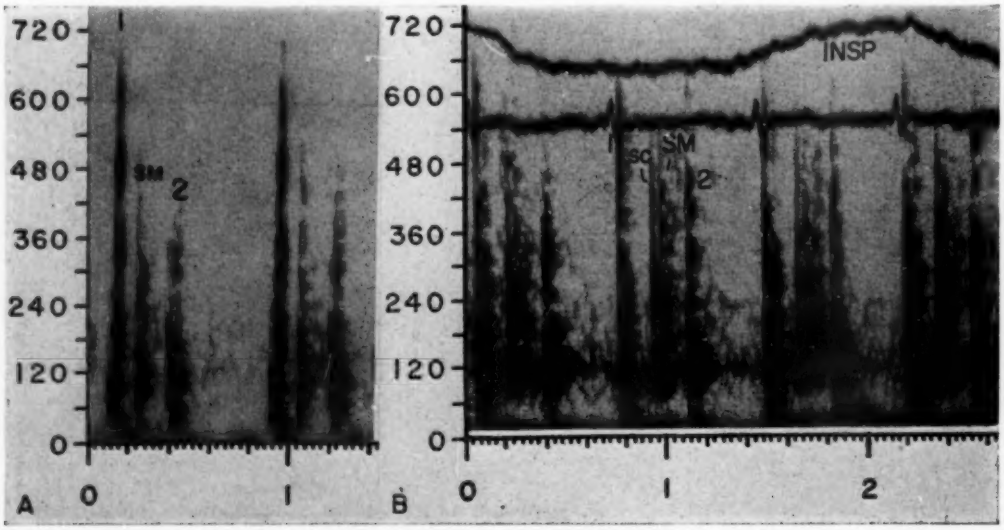


Fig. 15.—*Midsystolic Murmur Initiated by Systolic Click.* The patient whose apical recording is shown in *A* has Laennec cirrhosis. The patient whose recording at the left lower sternal border is shown in *B* has osteogenesis imperfecta with thoracic deformity (mainly kyphosis) on that basis. Note in each case the circumscribed systolic murmur which is initiated by a sharp clicking sound. This sonic phenomenon appears to result from pericardial adhesions and/or roughening. Evidence for a pericardial origin has been presented.[9,11]

Further features of note are as follows: In *A*, slight splitting of both sounds, particularly the second, is evident. The basis of the intensified and snapping component of the first sound is not clear. In *B*, the first sound is clearly split. Electrical interference (120 cycle) is present but is easily identified as such.

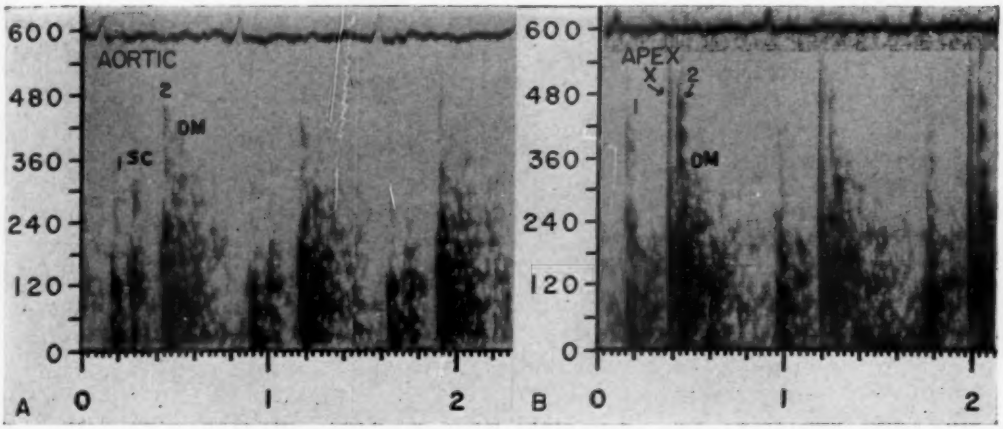


Fig. 16.—*Circumscribed Systolic Sounds in Syphilitic Aortitis With Aortic Regurgitation.* In the aortic area (*A*) of this patient there is demonstrated a decrescendo murmur in diastole beginning immediately with S_2. Early in systole there is a circumscribed sound marked "s.c." (systolic click) which is not actually a click as far as either its spectral pattern or the impression it made on the ear are concerned. To the ear there appeared to be wide splitting of the first sound. Although not as sharp and clicking as these sounds usually are, the fact that the patient has syphilitic aortitis with moderate dilatation of the ascending aorta makes it likely that this is the same type of sound as that which occurs with a dilated pulmonary artery and about which Leatham and Vogelpoel[12] have written recently.

At the apex (*B*) of this same patient there is a telesystolic click ("*X*"). In the spectrogram this is clearly a click because of its homogeneity of intensity-frequency pattern, its brevity, and the fact that its "frequency bottom" does not quite reach the base line as is the case with the valve closure sounds. To the ear this sound created the impression of a split second sound. In this instance the genesis of the late systolic click is unclear. As with the type of clicks demonstrated in Fig. 15 a pericardial origin has been suggested.[11]

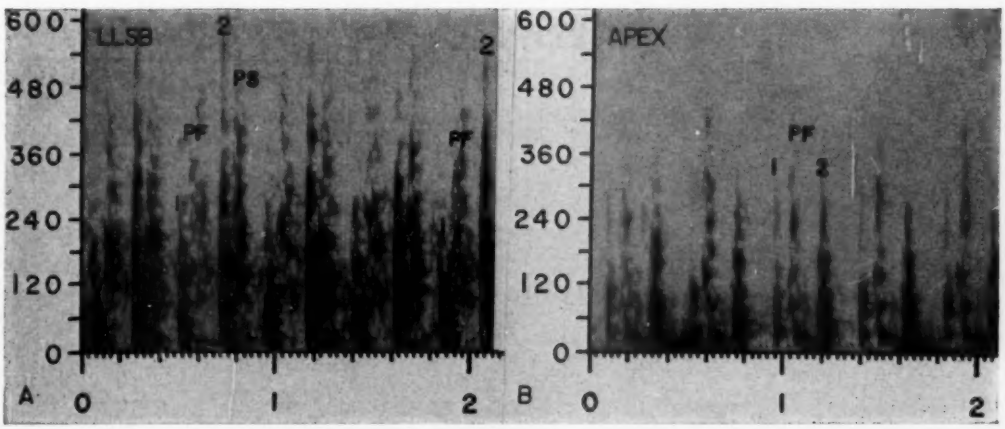


Fig. 17.—*Acute Tuberculous Pericarditis With Effusion and Moderate Cardiac Tamponade.* At the apex (*B*) the friction rub is limited to systole. However, it is easy to identify it as a rub rather than a murmur because of its quality as displayed here, just as the ear can usually make the same identification. At the lower left sternal border (*A*) there is a loud circumscribed sound in protodiastole which may be a pericardial friction rub but which more likely is an early protodiastolic sound of the type seen in constrictive pericarditis but also seen in cases of pericardial effusion with tamponade.[13] As is usually the case, this protodiastolic sound occurs slightly earlier than most protodiastolic gallops. In the period when the pericardial friction rub is disappearing, the component limited to systole may have a very musical quality with conspicuous harmonics and a croaking or creaking quality to the ear.

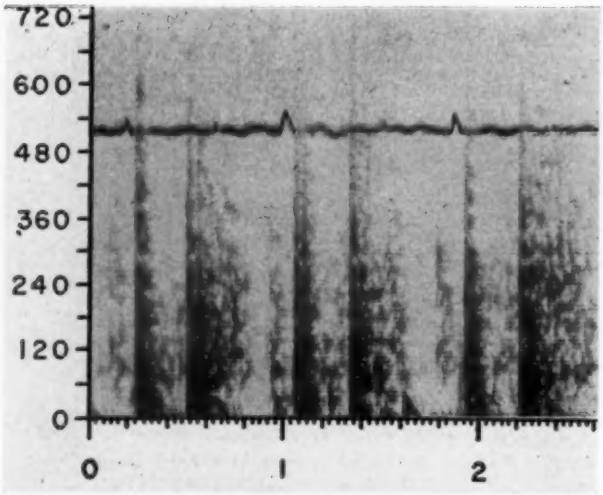


Fig. 18.—*Large Precordial Thoracic Cage Defect.* In this patient the costal cartilages and a large portion of the body of the sternum were removed in the several stages of cardiac decortication for constrictive pericarditis. The last operation was performed in 1951, and the patient is now free of symptoms of cardiac compression. The heart lies immediately beneath the skin. In most areas of the precordium, sounds indistinguishable from pericardial friction sounds are audible. It is these which are displayed here. The rub has three phases: systolic, protodiastolic, and presystolic. Residual roughening of the surface of the heart and its superficiality are considered to be the factors responsible for these sounds.

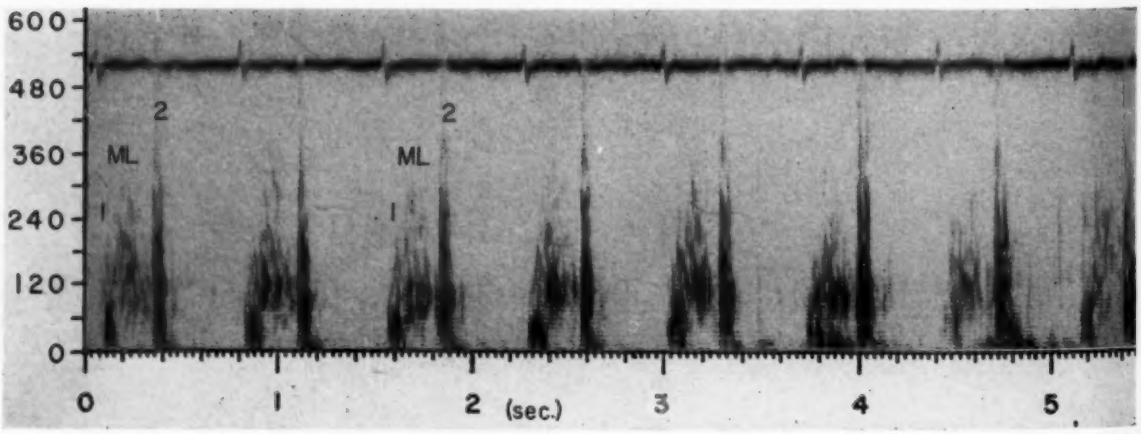


Fig. 19.—*Means-Lerman Scratch of Thyrotoxicosis.* This recording was made at the third left intercostal space of a patient with severe hyperthyroidism. A scratchy systolic sound was present. In order to display better the scratchy quality of the systolic murmur these analyses were made with filter system D rather than the customarily used filter system C.[1] (Filter system D has wider passband characteristics than C.) The systolic murmur ends before the end of systole. Its mechanism is thought to be dilatation of the pulmonary artery with flow through it increased both in volume and velocity. The second sound is split in some cardiac cycles.

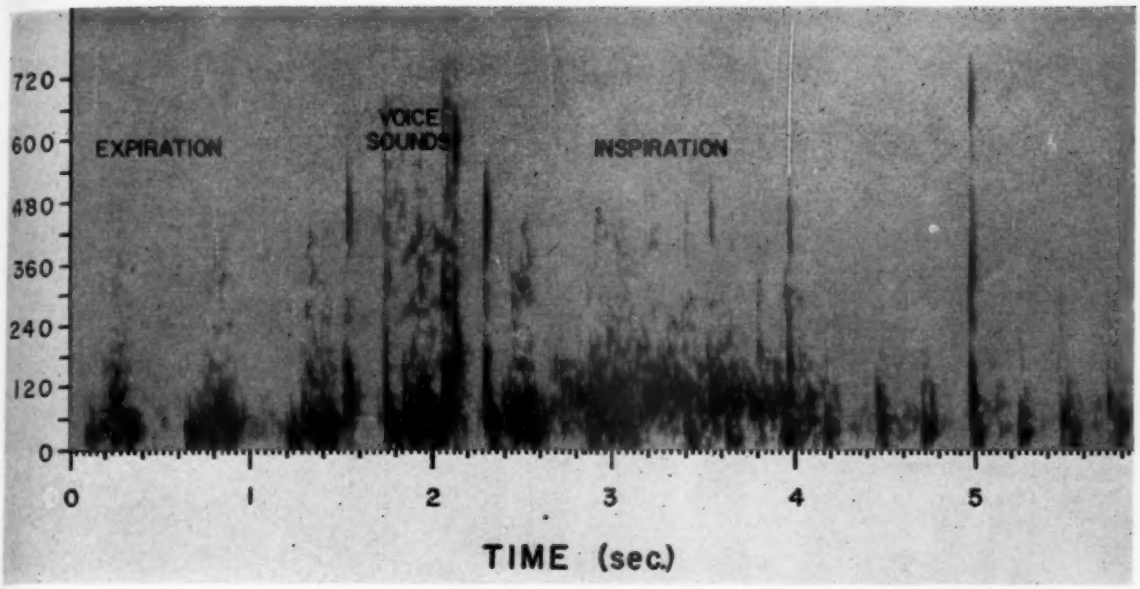


Fig. 20.—*Systolic Murmur Due to Pulmonary Artery Compression.* Here is shown a continuous recording from the pulmonary area of a patient with lymphosarcoma of the mediastinum: on the left in the normal expiratory chest position, and on the right in inspiration. A harsh systolic murmur, present in expiration, disappears with inspiration. The artifacts in the recording are spoken voice sound and breath sounds. Note the disappearance of the murmur with inspiration. Note further the splitting of the second sound which appears with inspiration. The murmur in this patient is believed to have been the result of pressure of a lymphosarcomatous mass on the pulmonary artery. Inspiration by increasing the capacity of the chest removed this compression. The murmur in this case has the typical appearance of an "ejection stenosis murmur" which, to be sure, it is. Its peak occurs later in systole than the peak of the ejection stenosis murmur of aortic origin, for instance.

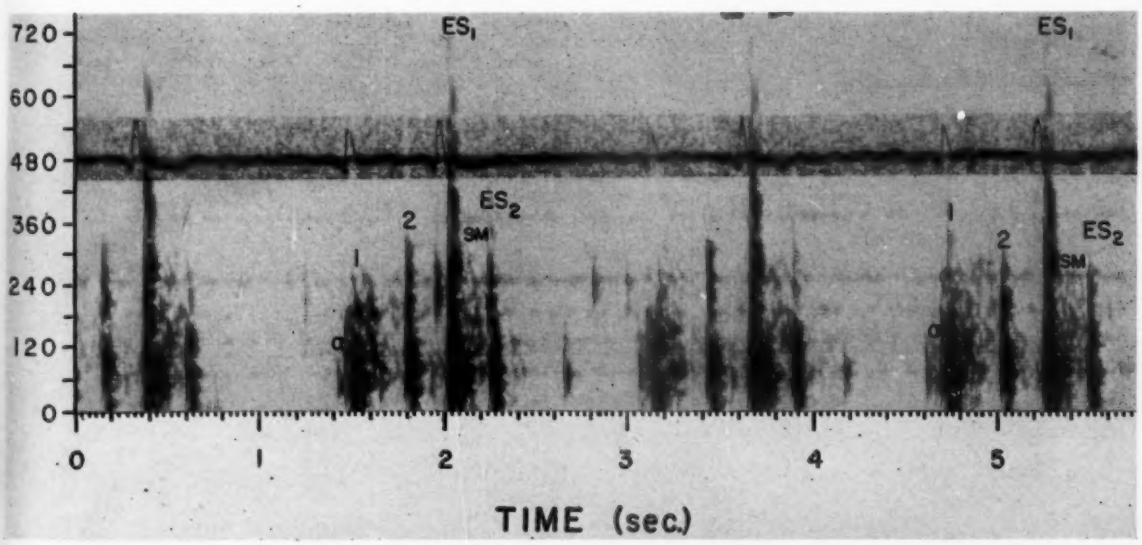


Fig. 21.—*Bigeminy.* Here is presented the recording from the aortic area in a patient with arteriosclerotic cardiovascular disease and pulsus bigeminus. Note that the extrasystolic first sound is greatly accentuated due probably to the wide open position of the A-V valves at the time the extrasystole occurs. Note secondly, that whereas in the normal cycles there is a sound which precedes the Q wave of the ECG, these are absent before the first sound of the ventricular extrasystoles. The atrium is, of course, inactive in the case of ventricular extrasystoles unless retrograde conduction occurs. In the third place, note that the second sound is usually diminished in the extrasystole as compared with the normal sinus beat. This is almost certainly related to low-stroke output and low-diastolic pressure with the extrasystole. Finally, note the considerable abbreviation of systole in the case of the premature beat. Systole is shortened mainly because of delay in the onset of the first sound. This delay is probably on the same basis as that seen with atrial fibrillation and is related in some way to the absence of preceding atrial contraction. The wider open position of the A-V valves may demand a longer time for closure. Note the 240 cycle electrical interference. Also, scattered through the record are four or five short sounds ("snaps" and "crackles") which are easily identified as artifacts.

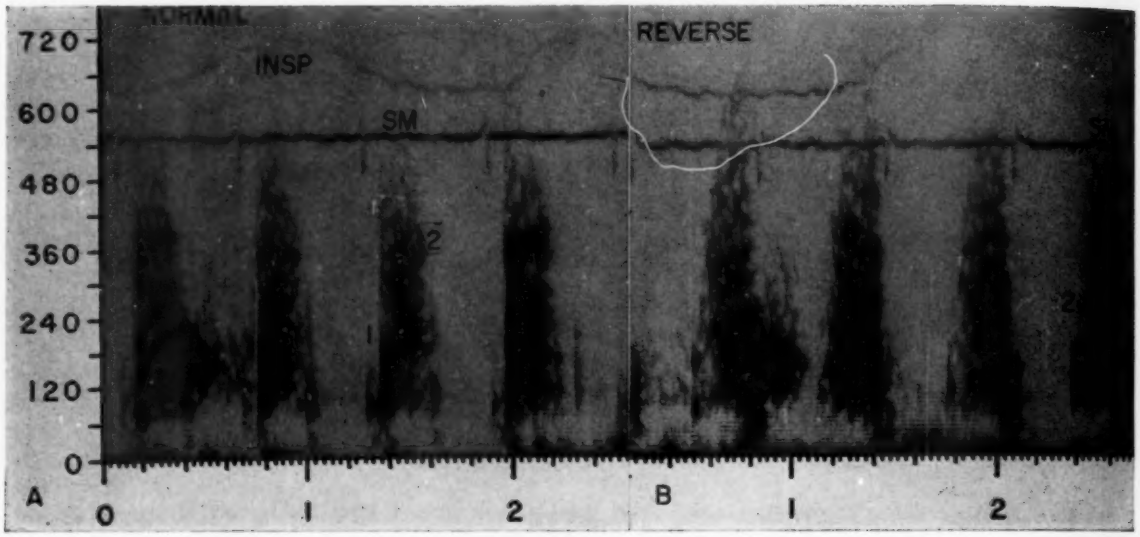


Fig. 22.—*A Filter Artifact.* The recordings are from the apex of a patient with rheumatic mitral regurgitation. When analyzed in the customary fashion, the beginning of the murmur (*A*) is seen to have a suspiciously sharp "front." We were suspicious that a threshold characteristic of the filter system is responsible for such sharp fronts, other instances of which may be present in some of the recordings earlier in this article. The same segment of sound was then played back in reverse into the analyzer. It is then seen that the sharp "front" is indeed largely artifact and that there is detail destroyed in the recording made in the usual manner. This artifact, fortunately, not too pronounced in the spectral phonocardiograph of current design, must be eliminated insofar as possible in future designs. Incidentally, playing of the tape recordings in reverse is useful in a case such as this in demonstrating the masking effect of the loud systolic murmur on the second sound which is slightly separated from it. Heard with difficulty when played in the normal manner, it was easily heard when the tape was played in reverse.

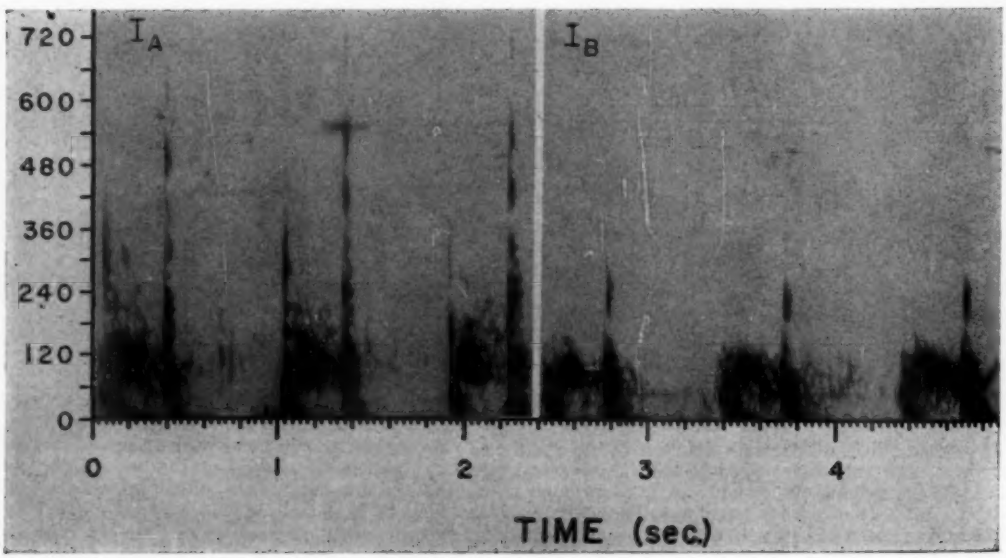
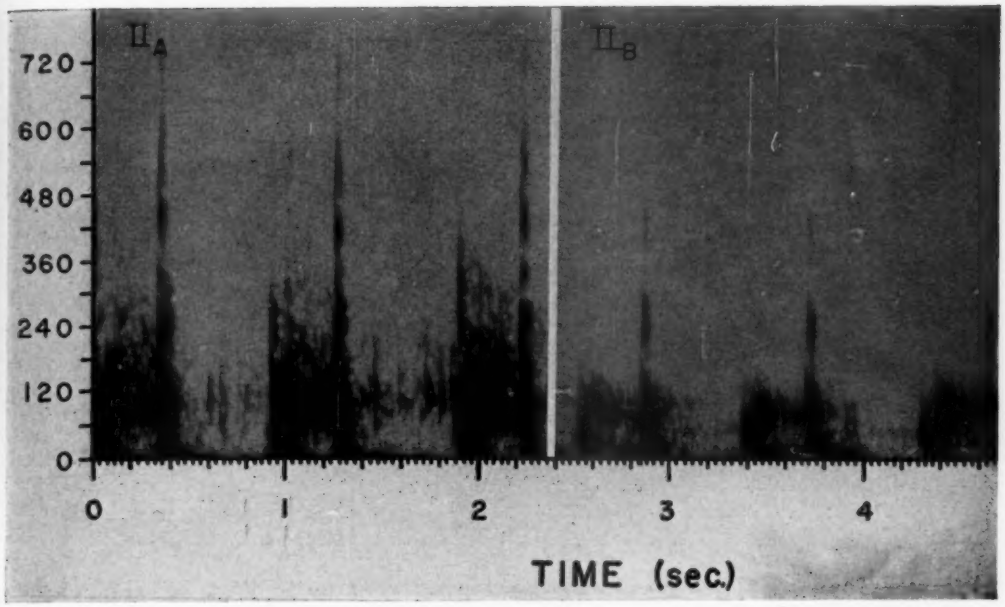
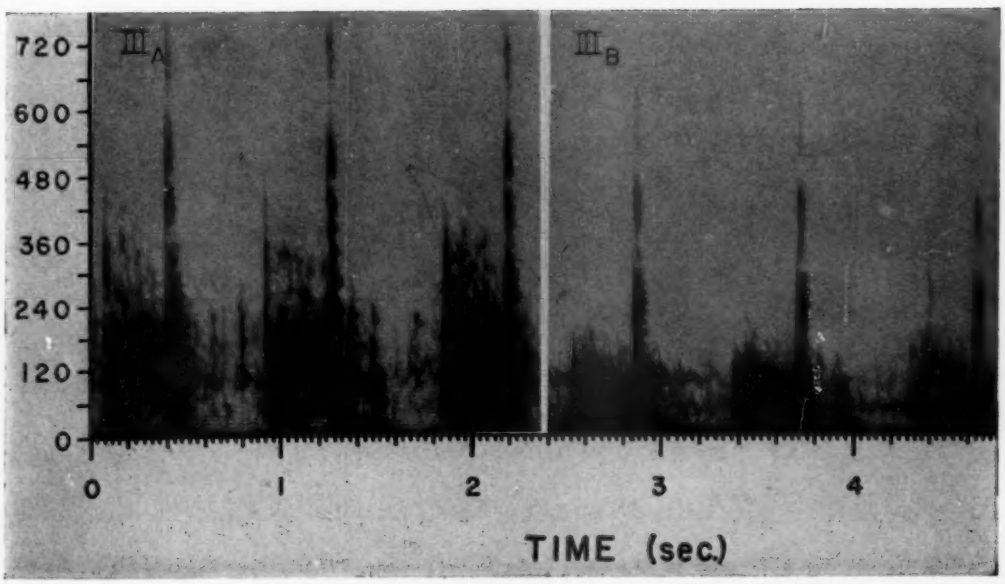


Fig. 23, *A*—*(For legend see page 931.)*



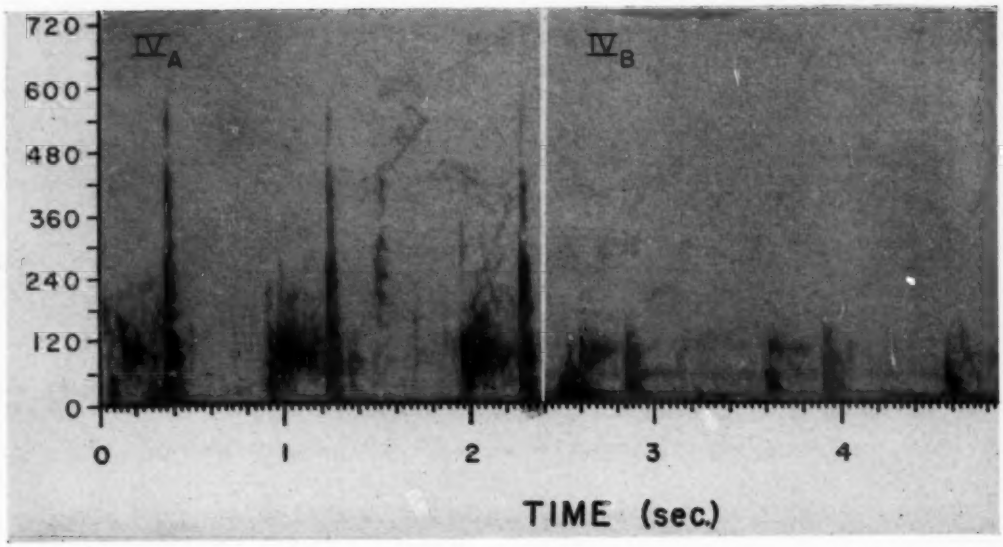
B.



C.

Fig. 23, *B* and *C*.—*(For legend see page 931.)*

D.



E.

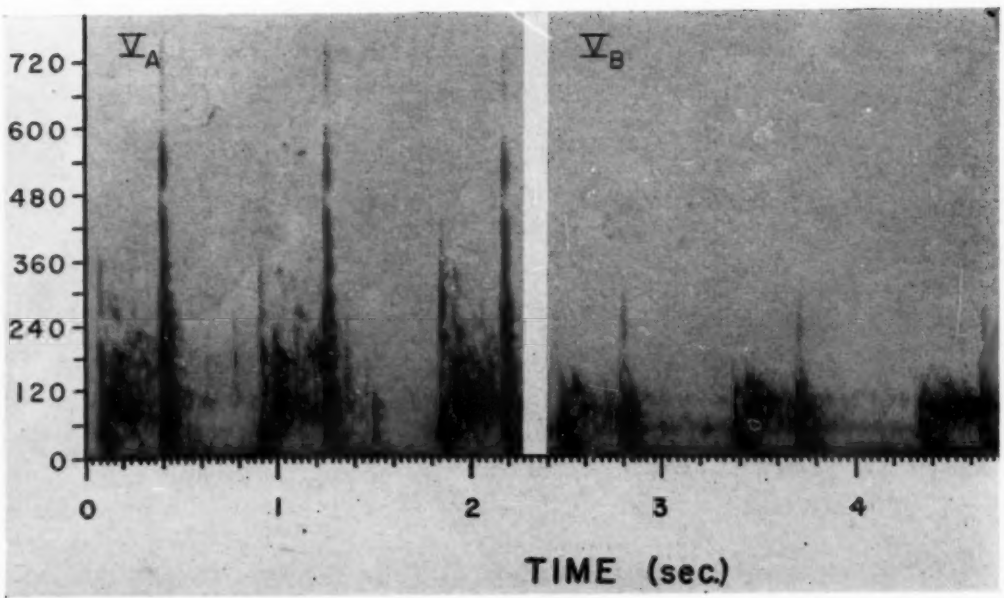


Fig. 23, *D* and *E*.—*(For legend see page 931.)*

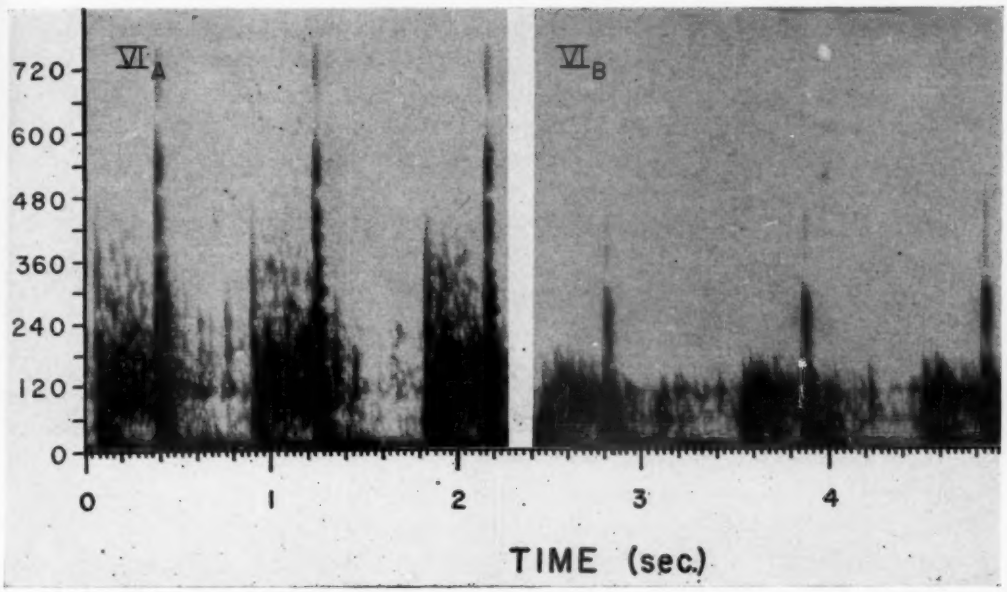


Fig. 23 *F*.

Fig. 23.—*Another Artifact of the Filter System.* The experiment represented by these recordings was suggested by our suspicions that artifactual high-frequency components are added by the filter system in the case of sharp sounds of high intensity. Recording *A* in each pair of records was made in the usual manner. Recording *B* was made after passing the sound through a pass-band filter which cut off components above 100 cycles. For analyses I, II, and III the sound was put onto the magnetic recording disk of the analyzer at the same level of amplification but was played back, during the analyses itself at three grades of amplification increasing from I to III. For analysis IV, V, and VI the sound was put through the analyzing filter system with the same amplification but in recording onto the magnetic disk of the analyzer three grades of amplification were used, increasing from IV to VI. (The sounds are from the pulmonary area of a 15-year-old boy with active rheumatic fever.)

The records demonstrate that, regardless of the stage at which additional amplification is applied, the analyzer displays frequencies appreciably above the level of cutoff of the pass-band filter when the sound is very loud. Whether the components of higher frequency so displayed are truly artifactual or not depends on whether the pass-band filter, which, of course, cannot be expected to cut off completely abruptly at 100 cycles, is likely to pass information up to 600 cycles, for instance, as in recording IIIB. This is, in fact, impossible with the pass-band filter employed which produces an attenuation of 24 db per octave. We are, then, dealing with a filter artifact which is again not pronounced if overloading is avoided. The artifact must be guarded against in filter design for spectral phonocardiography.

Since the artifact under discussion here does have basis in a cardiovascular event, it is an artifact only to the extent that the sound is misrepresented. Misrepresentation may be of two types: presentation of some true harmonic component in exaggerated proportions or the introduction of harmonics which are not present in the sound under analysis.

SUMMARY AND CONCLUSIONS

Demonstrated here is heart sound intensification of four types as to the principal factor (they are not mutually exclusive) responsible for the alteration. These four factors are as follows: (1) increased velocity of valve closure (Fig. 1); (2) increased force of valve closure (Fig. 2); (3) fibrosis and other physical change in the coapting valve cusps (Figs. 3, 6, 7, 8, 9, 10); (4) closure of valves from a wide-open position (Fig. 21).

Spectral phonocardiography improves greatly on the performance of conventional oscillographic phonocardiography in displaying the wide dynamic range of cardiovascular sound. Very loud murmurs and very faint ones can be simultaneously displayed in more nearly their true proportions (Figs. 4 and 5).

Also demonstrated are spectral phonocardiographic features of mitral stenosis (Figs. 6, 7, 8, 9, 10), mitral regurgitation (Figs. 11 and 12), aortic stenosis (Figs. 4 and 5), and aortic regurgitation (Figs. 3, 4, 5, and 16). Unusually high-pitched murmurs of aortic regurgitation (Figs. 4 and 5) and mitral stenosis (Fig. 7) are displayed. The diastolic rumble of mitral stenosis can vary in intensity with respiration (Fig. 8). The S_2-O.S. interval is unusually long in the combination of systemic hypertension and minimal mitral stenosis (Fig. 9). When atrioventricular conduction is delayed, the presystolic murmur may assume the Christmas tree appearance of an ejection stenosis murmur (Fig. 10). The holosystolic murmur of mitral regurgitation may be either decrescendo (Fig. 12,*A*) or crescendo (Figs. 11 and 12,*B*). It may continue directly into early diastole (Fig. 12,*B*). A prominent third heart sound is a usual accompaniment of mitral regurgitation (Figs. 11, 12,*A*). An opening snap may be present with overwhelmingly dominant mitral regurgitation (Fig. 11).

An atrial sound followed by an atrial murmur may occur in surgically induced complete heart block in dogs (Fig. 13).

Two types of quadruple rhythm are demonstrated (Fig. 14): (1) due to two atrial sounds with each ventricular cycle (2:1 heart block); (2) due to double gallops.

Two cases of midsystolic murmur initiated by a systolic click (Fig. 15) are presented, and the benign nature of this sonic phenomenon supported.

Systolic sounds, one in early systole due probably to syphilitic aortitis and one in late systole and probably of extracardiac origin, are demonstrated in the same patient (Fig. 16).

The characteristics of pericardial friction rubs are demonstrated (Figs. 17 and 18), as well as those of the Means-Lerman scratch (Fig. 19).

An ejection stenosis murmur due to pressure of a lymphosarcoma on the pulmonary artery disappeared with inspiration (Fig. 20).

In ventricular extrasystoles the first sound may be delayed and intensified and the second sound diminished (Fig. 21).

Splitting of the second heart sound is demonstrated (Figs. 6, 8, 9, and 20).

Two filter artifacts—"sharp fronts" and high frequency components—are analyzed. Although these artifacts are not great in the present method, improvement is possible and they must be recognized in future filter design for spectral phonocardiography.

SUMMARIO IN INTERLINGUA

Es illustrate cambiamentos del sonos cardiac in consequentia de (1) alterate velocitate del clausura valvular, como per exemplo post administration de epinephrina; (2) alterate fortia del clausura valvular, como per exemplo post cambiamentos in le pression arterial; e (3) alterate character physic del cuspides, como per exemplo in caso de fibrosis.

Phonocardiogrammas spectral pote esser arrangiate a coperir le large banda de intensitates del sonos cardiovascular; illos pote per exemplo exhibir in un sol registration le correcte proportiones de intensitate de un fortissime murmure systolic e de un debilissime murmure diastolic.

Es demonstrate (1) extraordinarimente alte murmures diastolic de regurgitation aortic e stenosis mitral; (2) decrescente e crescente murmures holosystolic e altere characteristicas de regurgitation mitral; (3) murmure e sono atrial in canes con complete dissociation atrioventricular inducite per medios chirurgic; e (4) systolic murmure rauc de thyrotoxicosis.

Es etiam discutite le sequente problemas technic: (1) le production de "frontes acute" in alciun sonos como function del structura del filtro e (2) le false addition de componentes a frequentia superior in intense sonos acute.

REFERENCES

1. McKusick, V. A., Talbot, S. A., and Webb, G. N.: Spectral Phonocardiography: Problems and Prospects in the Application of the Bell Sound Spectrograph to Phonocardiography, Bull. Johns Hopkins Hosp. **94**:187, 1954.
2. McKusick, V. A., Webb, G. N., Brayshaw, J. R., and Talbot, S. A.: Spectral Phonocardiography: Clinical Studies, Bull. Johns Hopkins Hosp. **95**:90, 1954.
3. McKusick, V. A., Webb, G. N., Humphries, J. O'N., and Reid, J. A.: On Cardiovascular Sound. Further Studies by Means of Spectral Phonocardiography, Circulation (In press).
4. Kjellberg, S. R., Rudhe, V., and Sjöstrand, T.: Influence of Autonomic Nervous System on Contraction of Human Heart, Acta Physiol. Scandinav. **24**:350, 1952.
5. Lamb, H.: The Dynamical Theory of Sound, Ed. 2, London, 1931, Edwin Arnold & Co., pp. 74-75.
6. Foulger, J. H., Smith, P. E., Jr., and Fleming, A. J.: Cardiac Vibrational Intensity and Cardiac Output, Am. Heart J. **35**:953, 1948.
7. Wills, B.: The Assessment of Mitral Stenosis by Phonocardiography, Brit. Heart J. **16**:261, 1954.
8. Kuo, P. T., and Schnabel, T. G., Jr.: Phonocardiography in the Differentiation of Predominant Mitral Regurgitation From Predominant Mitral Stenosis, Presented at Second World Congress of Cardiology, Washington, D. C., Sept. 16, 1954.
9. Messer, A. L., Cournihan, T. B., Rappaport, M. B., and Sprague, H. B.: The Effect of Cycle Length on the Occurrence of the First Heart Sound and the Opening Snap in Mitral Stenosis, Circulation **4**:576, 1951.
10. Rytand, D. A.: An Auricular Diastolic Murmur With Heart Block in Elderly Patients, Am. Heart J. **32**:579, 1946.
11. Gallavardin, L.: Nouvelle observation avec autopsie d' un pseudo-dédoublement du 2e bruit du coeur simulant le dédoublement mitral par bruit extra-cardiaque télésystolique surajouté, Prat. méd. franç. **13**:19, 1932.
12. Leatham, A., and Voegelpoel, L.: The Early Systolic Sound in Dilatation of the Pulmonary Artery, Brit. Heart J., **16**:21, 1954.
13. McKusick, V. A., and Harvey, A. M.: Diseases of the Pericardium, Adv. Int. Med. **7**: 1955.

VENTRICULAR ANEURYSMS OF THE HEART

Preliminary Report on Some New Clinical Signs

Rustom Jal Vakil, M.D. (Lond.)

Bombay, India

ALTHOUGH the first authentic case of cardiac aneurysm was reported by Hunter[9] in 1757, Remlinger[15] in 1896 was the first to diagnose the condition correctly, during life, on the basis of a musical, to-and-fro murmur. Until the year 1926, only six cases of cardiac aneurysm had been correctly diagnosed ante mortem (Pletnew[14]).

In spite of the comparative rarity of ventricular or parietal aneurysms of the heart, a massive literature on the subject is in existence, as shown by recent reviews (Sternberg[18]; Parkinson and associates[13]; Vakil[21]).

Although the diagnostic value of clinical signs in cardiac aneurysms has been minimized by several authors in the past (Hall[5]; Sternbert[18]; Lutembacher[11]; Christian and Frik[2]; Strandell[19]), the great majority of present-day authorities are convinced of the diagnostic significance of at least some of these signs. Dressler and Pfeiffer[3] were able to diagnose the condition correctly, by recourse to the pulsatory signs alone, in nine out of their ten cases.

In view of the prevalence of coronary thrombosis, it is only natural that the entity of ventricular aneurysm of the heart should attract more attention today than in the past. Under the circumstances, any new sign or clinical feature that is likely to facilitate its recognition during life bears investigation.

In a recent study of twenty proved cases of ventricular or parietal aneurysms of the heart (Vakil[21]), reference was made, in the course of discussion, to certain new or hitherto undescribed, clinical signs of diagnostic value. These signs were considered noteworthy in view of their suggestive character or frequency of occurrence. It is with a view to stimulate further inquiry or investigation into this matter that the following brief description of these signs is presented.

ABNORMALITIES OF THE CARDIAC IMPULSE

Abnormalities of cardiac pulsation have been frequently described in the literature on ventricular aneurysms of the heart. Thus Strauch[20] described a systolic thrust in the mesocardial region, Pletnew[14] stressed the existence of a

From the Cardiac Department, King Edward Memorial Hospital, Bombay, India.
Received for publication Jan. 4, 1955.

heaving pulsation of the whole precordium, Libman and Sacks[10] described a pulsation between the apex of the heart and the sternum, East[4] noted a wavy pulsation of the precordium in two of his cases, and Harvier and Caroli[6] described a systolic retraction of the intercostal spaces at the site of the aneurysm. The simultaneous existence of two cardiac thrusts, apical and mesocardial, has been described by numerous observers (Huchard[8]; Strauch[20]; Shennan and Niven[17]; Libman and Sacks[10]; Harvier and Caroli[6]; Heim de Balsac[7]; Parkinson and associates[13]). A large, forceful, and remarkably wide cardiac thrust, in the vicinity of the left mid-clavicular line and usually on a level with the fifth rib, has been described as a characteristic finding by Dressler and Pfeiffer.[3]

ANOMALOUS LOCATION OF THE CARDIAC IMPULSE

In ten of my cases of ventricular aneurysms, the cardiac impulse or thrust displayed the following characteristic location.

Instead of a normally situated apical impulse, a very wide or diffuse, systolic thrust or pulsation, forcible and heaving in character, was seen and felt at the level of the fourth left intercostal space, halfway between the left parasternal and mid-clavicular lines. The clinical impression imparted in such cases was that of marked inward displacement of the apical impulse, all the more striking in virtue of the outward displacement of the left cardiac border demonstrable on percussion.

OTHER ABNORMALITIES OF THE CARDIAC IMPULSE

Inspection and palpation of the cardiac impulse revealed, in the majority of my cases of ventricular aneurysm of the heart, abnormalities in character which have apparently not been described previously in the literature.

In thirteen cases (or 65 per cent), clinical examination of the cardiac impulse in the recumbent posture, both on inspection and palpation, revealed an extraordinary slowness (or "lag") of the up-and-down movement of the chest wall with each beat of the heart. This was particularly noticeable during the downward movement or retraction of the chest wall. The term myotonic impulse is suggested as a suitable designation for this effect, since it best describes the sign. To determine the specificity of the sign, the cardiac impulse was subjected to a similar scrutiny in other types of cases, both cardiac and noncardiac; although, a "lag" of upward movement of the chest wall, at the site of the cardiac impulse, was demonstrable in some cases of left ventricular hypertrophy, a similar abnormality of downward movement was never observed.

Either in conjunction with the sign described above or independently of it, other forms of abnormality of the cardiac impulse were demonstrable in ten (or 50 per cent) of my cases. Of these cases, four displayed a characteristic double-thrust or reduplication of the impulse, easily perceived by the palpating hand. In the remaining six cases, the cardiac impulse displayed a peculiar undulating or wavelike character, particularly on palpation. To describe this effect, the following alternative designations are suggested, namely, cardiac shudder or wavy impulse.

Heaving Left Costal Margin.—In two (or 10 per cent) of my cases of ventricular aneurysm of the heart, the correct diagnosis was primarily suggested by a characteristic heaving, up-and-down movement, of the left costal margin (synchronous with the heart beat), best seen and felt with the patient in the supine position; this was associated, in both cases, with (1) a relative craniad shift of the left costal margin, and with (2) a visible and palpable pulsation in the region of the left hypochondrium and epigastrium, just below the left costal margin.

Area of Stony Dullness.—Although an increased area of cardiac dullness has been stressed, in the past, as a sign of cardiac aneurysm by Huchard,[8] Aubertin and Lerebouillet,[1] and Strandell,[19] this sign has lost its significance in view of the fact that it may be encountered in a host of cardiovascular diseases.

In my series of cases of ventricular aneurysms, I was impressed more by the degree of dullness on percussion over the left side of the precordium than by an increased extent of dullness. In nine of my cases (45 per cent) of ventricular aneurysm of the heart, the degree of impairment of percussion note was severe enough to approximate the stony dullness, elicitable over serous effusions.

A Musical Systolic-diastolic Murmur.—Murmurs, both systolic and diastolic, have figured prominently in the literature on cardiac aneurysms. A systolic murmur at the apex has been described by Aubertin and Lerebouillet,[1] Strandell,[19] and by Parkinson and associates,[13] a postsystolic murmur by Huchard,[8] Padilla and Cossio,[12] and by Scherf and Erlsbacher,[16] and a double murmur by Remlinger,[15] Strauch,[20] Scherf and Erlsbacher,[16] Aubertin and Lerebouillet,[1] and by Strandell.[19]

In five (25 per cent) of my cases, a murmur with the following characteristics was observed, namely, a fairly loud and long murmur, with a peculiar "cooing," "plaintive," or musical character, occupying the whole of systole and early part of diastole, best heard at the site of the cardiac impulse, and not conducted in any particular direction.

SUMMARY

In the course of investigation of twenty proved cases of ventricular aneurysm of the heart, the following clinical signs, hitherto undescribed in the literature, were discovered, namely, (1) an anomalous location of the cardiac impulse (50 per cent of cases), (2) a myotonic cardiac impulse (65 per cent), (3) a double thrust or reduplicated impulse (20 per cent), (4) a wavy impulse or cardiac shudder (30 per cent), (5) a heaving left costal margin, (6) stony dullness over the precordium, and (7) a loud and long, musical or "cooing" systolic-diastolic murmur. These signs are briefly described with a veiw to stimulate further inquiry into the matter.

SUMMARIO IN INTERLINGUA

In le curso del investigation de 20 confirmate casos de aneurysma ventricular del corde, le sequente signos clinic, non previemente describite in le litteratura, esseva discoperite: (1) Un anormal loco del impulso cardiac (50 pro cento

del casos), (2) un impulso cardiac myotonic (65 pro cento), (3) un impulso reduplicate (20 pro cento), (4) un impulso undiforme (30 pro cento), (5) un movimento in alto e in basso, synchrone con le battimento del corde, del margine costal al latere sinistre, (6) un percussion surde super le pericordio, simile al percussion audite super effusiones seral, e (7) un forte e longe murmure systolic e diastolic, de character plangente e musical.

Iste signos es describite brevemente pro stimular plus extense investigationes del question.

REFERENCES

1. Aubertin, C., and Lerebouillet, J.: Arch. des maladies du coeur, **24**:465, 1931.
2. Christian and Frik: Klin. wchnschr. **1**:582, 1922.
3. Dressler, W., and Pfeiffer, R.: Ann. Int. Med. **14**:100, 1940.
4. East, T.: Proc. Roy. Soc. Med. **26**:518, 1933.
5. Hall, D. G.: Edin. Med. and Surg. Jour. **14**:322, 1903.
6. Harvier, P., and Caroli, J.: Paris méd. **77**:30, 1930.
7. Heim de Balsac, R.: L'anevrysme pariétal du coeur, Paris, 1938, Gaston Doin & Cie.
8. Huchard, H.: Traite Clinique des Maladies du coeur et de L'Aorte, Paris, 1899, Gaston Doin & Cie.
9. Hunter, J.: An Account of the Dissection of Morbid Bodies, Ms cop. **32**:30, 1757.
10. Libman, E., and Sacks, B.: Am. Heart J. **2**:321, 1926.
11. Lutembacher, R.: Arch. mal. coeur. **13**:49, 1920.
12. Padilla, T., and Cossio, P.: Rev. de la Soc. de Med. Interna et de la Soc. de Fisiol. **6**:385, 1930.
13. Parkinson, J., Bedford, E. D., and Thomson, W. A. R.: Quart. J. Med. **7**:455, 1938.
14. Pletnew, D. D.: Ztschr. klin. Med. **104**:378, 1926.
15. Remlinger, P.: Bull. med. **10**:483, 1896.
16. Scherf, D., and Erlsbacher, O.: Med. Klin. **30**:1687, 1934.
17. Shennan, T., and Niven, W.: J. Path. & Bact. **28**:390, 1925.
18. Sternberg, M.: Das chronische Partielle Herzaneurysma, Leipzig, 1914.
19. Strandell, B.: Acta med. scandinav. **74**:148, 1930.
20. Strauch: Ztschr. klin. Med. **41**:231, 1900.
21. Vakil, R. J.: Medicine **1**:1, 1954.

Announcement

The 12th Brazilian Congress of Cardiology will be held in Sao Paulo July 3 to 10, 1955.

Erratum

On page 413 of the March, 1955, issue in the article "Oral Mercurial Diuretics: Mercumatilin in the Treatment of Congestive Heart Failure," by Sim P. Dimitroff, Rand C. Lewis, M. C. Thorner, and John B. Field, reference 5 should be Vander Veer, J. B., Clark, T. W., and Marshall, D. S., II: The Prolonged Use of an Oral Mercurial Diuretic in Ambulatory Patients With Congestive Heart Failure, Circulation **1**:516, 1950.

Book Reviews

SELECTED PAPERS OF DR. FRANK N. WILSON. Edited by Franklin D. Johnston and Eugene Lepeschkin. Ann Arbor, Mich., 1954, J. W. Edwards, Publisher, Inc.

It is one of the misfortunes of present day cardiology that Frank Wilson's fundamental contributions were never assembled by himself into book form. It is known that at one time he intended doing this but was prevented by his reluctance to leave his investigative work for the necessary period in the editor's chair.

The present volume is made up of a collection of Wilson's most important papers (53 of them, comprising more than 1,000 pages) and has been compiled as a labor of love by two of his closest associates. It is undoubtedly the best possible substitute for the missing book. The papers are grouped under several headings: Theory of Electrocardiographic Leads, Genesis of the Electrocardiogram, The T Wave and the Ventricular Gradient, The Ventricular Complex in Myocardial Infarction, Bundle Branch Block. There are a few papers on cardiac arrhythmias. Our only criticism is that there is no index.

Wilson's contributions to modern cardiology are of its very essence, and even to consider reviewing them here would be presumptuous. Suffice it to say that not only for its value as the record of a great investigator's labors and thoughts, but also for its very real usefulness as a reference work, this book deserves a place in the libraries of all practitioners and teachers of cardiology.

J.H.P.

ATLAS OF CONGENITAL CARDIAC DISEASE. By Maude E. Abbott, B.A., M.D., F.R.C.P. (Canada). Facsimile reprint of original edition (1936), published by The American Heart Association, Inc., New York, 1954, 62 pages.

The American Heart Association, Inc. is to be congratulated on its initiative and historical outlook in publishing a facsimile of the original edition of this valuable atlas, too long out of print. Such a move does honor to the memory of the late Dr. Abbott, who for so many years carried almost single-handed the torch for a subject long considered academic, curious and impractical, fit only for the gloomy pathologic museums of the time.

This atlas is a monument to a lifelong interest, an interest which supplied the groundwork for the present amazing advances in diagnosis and treatment. Yet Dr. Abbott's anatomic knowledge alone would not have been sufficient to keep the subject alive if it had not been combined with clinical interest and acumen. She was not content to preach from the laboratory but went farther to invade the haunts of the clinicians and attempt clinicopathologic correlation. This aspect is a feature of the atlas.

It is not the purpose of this review to present a criticism of the atlas, as that was done with the original edition and is a matter of record. It is well to recall, however, certain features of this monograph.

This is the reprinting of an historical document and a summation of knowledge as of the year 1936. For the younger student of congenital heart disease it will supply the historic background to give him a well balanced outlook on modern advances. The clinical classification of the cyanotic, acyanotic, and "cyanose tardive" groups still stands the test of time and has been proved in principle by modern methods. The brief introductory part on development and comparative anatomy serves to remind us of the miracle of normal development preceded as it is by the fleeting stages of phylogenesis. The embryology may be outmoded, but the author's descriptions emphasize that for the complicated anomalies no satisfactory substitute has been forthcoming.

The remainder of the atlas is a good presentation of various anomalies, well illustrated by excellent drawings and diagrams with sufficient clinical, radiologic, and electrocardiographic data to say that this is indeed a clinicopathologic atlas.

For the older student of cardiac anomalies this still stands as a valuable reference book, often referred to. Even yet it amazes the reviewer to find illustrative examples of unusual cases, descriptions of which are difficult to discover in the literature. The American Heart Association has indeed rendered a valuable service in making this volume available to all students of the subject.

F.W.W.

VERHANDLUNGEN DER DEUTSCHEN GESELLSCHAFT FÜR KREISLAUFFORSCHUNG. Edited by Professor Dr. Rudolf Thauer, Darmstadt, 1954, Dr. D. Steinkopff, pp. 408.

The proceedings of the 20th annual meeting of the German Society for Circulation Research give an excellent cross section of the present state of research in Germany on acquired valvular disease, endocarditis, and phonocardiography, which were the topics selected for major discussion. The initial paper by C. J. Wiggers (Cleveland) on hemodynamic problems of experimental valvular lesions is one of the best condensed reviews of the fundamental work carried out by the author and his associates over a period of three decades (pp. 3-19). A review of the clinical aspects of acquired valvular disease, presented by F. Grosse-Brockhoff (pp. 19-43), is followed by K. Blumberger's paper (pp. 43-57) on hemodynamics in valvular heart disease. The latter contains a very instructive summary in tabular form of the most important hemodynamic changes in aortic and mitral stenosis and insufficiency. E. Derra discusses the current status of surgical technique (pp. 57-71), and O. Boyer (pp. 72-93) the indications for valvular surgery.

A review of the pathology of endocarditis by R. Böhmig (pp. 160-176) is followed by P. Klein's discussion of the bacteriology and immunology (pp. 176-191). Finally the clinical aspects of endocarditis are presented by R. Hegglin (pp. 191-207). F. Wuhrmann (pp. 208-224) presents recent data on humoral and cellular changes in the blood in different types of endocarditis which emphasize changes of α, β, and γ globulins. K. Fellinger (pp. 225-232) found a substantial transient increase of endocarditis mainly in the male population in Vienna during the postwar period. It was thought to be probably due to an increase in exposure and stress. The course was comparatively mild, but there was a higher incidence of renal complications. This observation is of interest because it contrasts with the lower incidence of degenerative heart disease in the post-war period in Europe.

The third topic, phonocardiography, is opened by F. Trendelenburg's review (pp. 240-304) of its physical basis and followed by E. Schütz's thorough analysis of the physiologic background, with emphasis on the time relationships between heart sounds and other mechanical events. The diagnostic value of the phonocardiogram is discussed by A. Weber (pp. 339-355) and K. Holldack (pp. 355-364), and recent technical progress by H. Maass (pp. 326-339), particularly concerned with amplitude frequency characteristics.

In the limited space of this review, it is not possible even to list the numerous shorter presentations at the meeting. A total of 39 papers were read. In general, their standard is high, and the results are of definite interest for all engaged in circulatory research and application to clinical problems. The quality of the numerous illustrations is excellent.

E.S.

CURRENT CONCEPTS IN DIGITALIS THERAPY, A GUIDE TO THE USE OF DIGITALIS DRUGS. By Bernard Lown, M.D., and Samuel A. Levine, M.D. Boston, 1954, Little, Brown and Company, 164 pages.

Although digitalis has been standard therapy in the treatment of heart disease since the days of Withering, it becomes necessary from time to time to take stock of the new information and correlate it with the old. A review of current concepts supported by a bibliography of over 300 references is therefore most welcome. The authors of this small monograph and their qualifications are well known to all cardiologists. The mechanism of action is considered briefly but adequately in the first chapter. One chapter is taken up entirely with the subject of digitalis intoxication. The authors view with alarm the rising incidence of digitalis toxicity. It is their opinion that this is due largely to rapid intravenous digitalization and to oversimplification in dosage of oral digitalization, particularly in the administration of the cardiac glycosides where

" . . . a single-dose method for digitalizing with digitoxin has been promulgated." Another reason is the increasing dependence of treatment on electrolyte manipulation by restriction of salt-intake, administration of mercurial diuretics, carbonic acid anhydrase inhibitors, etc. Electrolyte shift, particularly in regard to potassium, will significantly alter the patient's tolerance to digitalis and complicate the problem of digitalis dosage and toxicity. An excellent chapter on electrolytes and digitalis explains this problem very well.

Only brief reference is made to the various cardiac glycosides which are now so commonly used in this country. Since this book stresses current concepts, more space might have been alloted to substances in current use. One cardiotonic substance, namely, acetyl strophanthidin, is given more emphasis than it deserves. This substance has an extremely short latent period, achieves its peak effect in a matter of minutes, and is very rapidly dissipated. The authors describe a digitalis tolerance test using acetyl strophanthidin, 0.3 mg. every five minutes intravenously, until either a therapeutic effect or mild toxicity occurs. Such a test would appear to be dangerous in those patients that might already be toxic from digitalis, and in those patients that are known to be underdigitalized such a test would not be necessary.

In general, this small monograph presents an accurate summary of our present knowledge of digitalis and its clinical use, and is a good reference book for the cardiologist.

A.C.D.

MYOCARDIAL INFARCTION: ITS CLINICAL MANIFESTATIONS AND TREATMENT WITH ANTICOAGULANTS. By Irving S. Wright, M.D., Charles D. Marple, M.D., and Dorothy Fahs Beck, Ph.D. (Published for the American Heart Association) New York, 1954, Grune & Stratton, Inc., 656 pages.

This book is actually a report to the American Heart Association of a committee appointed to study the use of anticoagulants in myocardial infarction. There have been, in fact, two such committees. The first one, appointed in 1946, consisted of the physicians in charge of the services in the hospitals participating in the study with Dr. Irving S. Wright, chairman, Dr. Charles Marple, coordinator, and Dorothy F. Beck, statistician. An entirely new committee retaining only the same chairman and statistician came into being in 1950. It is this latter committee which has now presented its report in such detail that it has taken the form of a large volume.

Care was taken in setting up the original study that the data obtained would be statistically sound, and the participating hospitals were required to submit information on each case studied, whether control or treated, in a uniform manner. The first five chapters of the book are concerned with the manner of setting up the study, the type of records used, and the way in which controls were established. Much information on the natural history of myocardial infarction aside from the effect of anticoagulants was obtained. The inclusion of these data is one of the reasons for the bulkiness of the report. Some of this material might well have been omitted. For instance, there is one chapter on the relationship of the onset of myocardial infarction to effort. It is obvious from reading this chapter that data obtained were quite sketchy in this regard and of no real value. There are several good studies already available designed specifically to get information on the exact amount of work preceding myocardial infarction. The book would have been much better and considerably shorter, then, if restricted to the question as to the value of anticoagulants in myocardial infarction.

The committee favors the use of anticoagulant therapy in all cases of myocardial infarction except where contraindications such as, blood dyscrasias, hypertension, peptic ulcer, and other situations which might produce dangerous bleeding, are present. The data indicate not only a lower mortality in the treated group as compared with the controls but also a decided decrease in thromboembolic complications.

The text is supplemented by numerous diagrams and tables. Many additional tables are included in an appendix. The literature is well reviewed, and there is an excellent bibliography of 267 references. A good index makes the material in the book easily available for reference. This is the most thorough and complete presentation yet published on the controversial subject of anticoagulants in myocardial infarction. It should be available for reference to every cardiologist.

A.C.D.

INDEX TO VOLUME 49

AUTHORS INDEX

N

O

P

R

SUBJECT INDEX

D

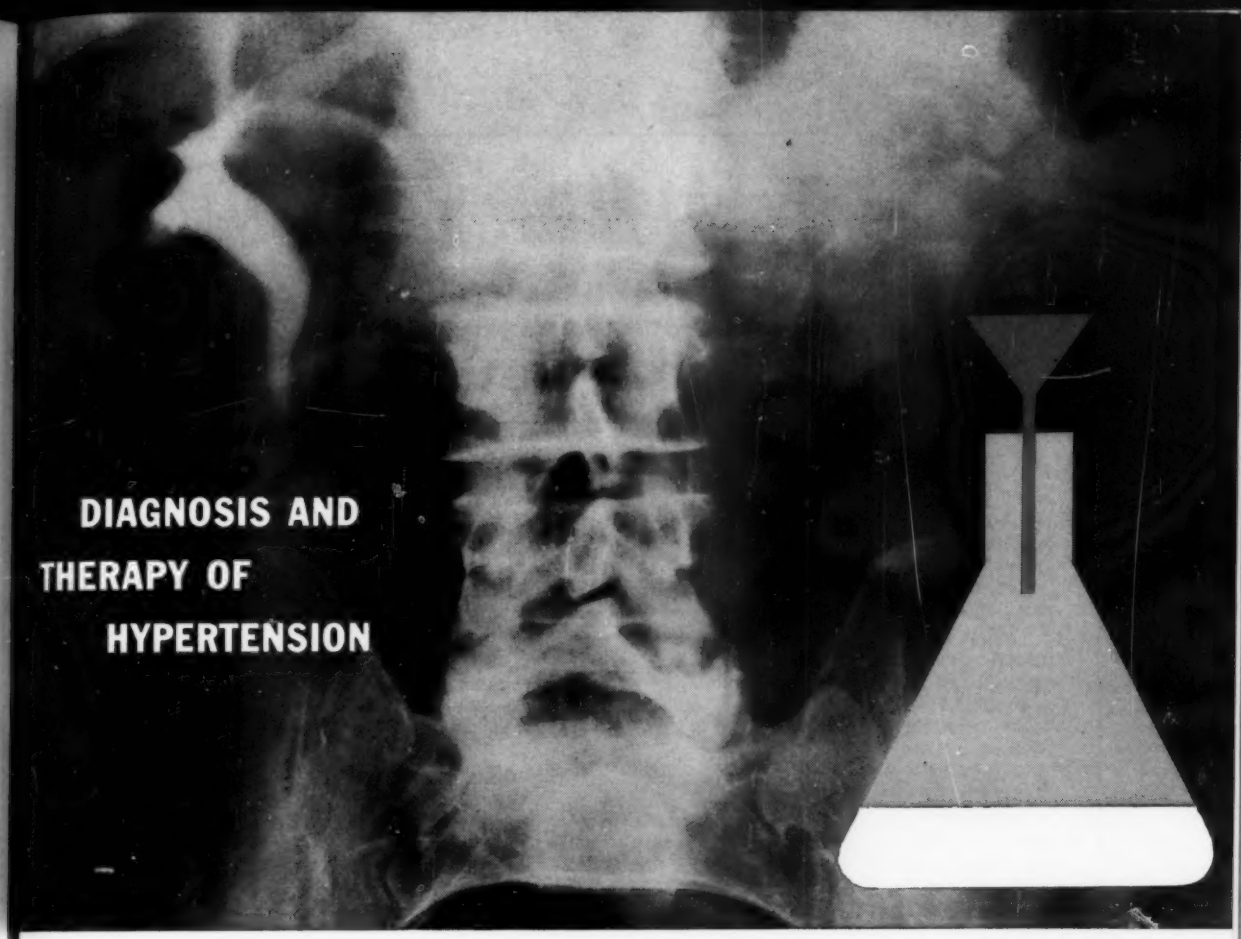
T

U

V

W

Z



kidney damage

In the diagnosis of hypertension, kidney damage can be recognized by *two* commonly used methods: blood chemistry may indicate functional inadequacy; the retrograde pyelogram reveals structural damage.

In the therapy of hypertension, also, *two* agents may be used for better control and greater safety. Methium with Reserpine combines the potent ganglionic blocking action of hexamethonium with the mild hypotensive and sedative effects of reserpine. "...this combination accomplishes a more stable reduction of blood pressure than that achieved with hexamethonium alone."* Synergism between the two agents permits reduced dosages, thus minimizing the risk of side effects.

Because of the potency of Methium, careful use is required. Caution is indicated in the presence of renal, cardiac or cerebral arterial insufficiency. Markedly impaired renal function is usually a contraindication.

Supplied: *Methium* 125 *with Reserpine*—scored tablets containing 125 mg. of Methium and 0.125 mg. of reserpine. *Methium* 250 *with Reserpine*—scored tablets containing 250 mg. of Methium and 0.125 mg. of reserpine.

*Dennis, E.; McConn, R. G.; Ford, R. V.; Hughes, W. M.; Beazley, H. L., and Moyer, J. H.: Postgrad. Med. *16*:300 (Oct.) 1954.

Methium® with Reserpine

CHLORIDE

(BRAND OF HEXAMETHONIUM CHLORIDE)

"a perfect match"

WARNER-CHILCOTT

American Heart Journal

For the Study of the Circulation

JONATHAN C. MEAKINS, M.D., Editor

3640 University Street, Montreal, Canada

PUBLISHED BY THE C. V. MOSBY COMPANY, 3207 WASHINGTON BOULEVARD, ST. LOUIS 3

EDITORIAL COMMUNICATIONS

Original Communications.—Manuscripts for publication, letters, and all other communications relating to the editorial management of the Journal should be sent to the Editor, Dr. Jonathan C. Meakins, 3640 University Street, Montreal 2, P.Q., Canada. Articles are accepted for publication with the understanding that they are contributed solely to the American Heart Journal.

Neither the editor nor the publisher accepts responsibility for the views and statements of authors whose manuscripts are published as "Original Communications."

Manuscripts.—Manuscripts should be typewritten on one side of the paper only with double spacing and liberal margins. References should be placed at the end of the article and should consist of the name of the author, the title of the article, and the name, volume number, page number and year of publication of the journal, in that order. Illustrations accompanying manuscripts should be numbered, provided with suitable legends, and marked lightly on the back with the author's name.

A brief abstract of the article (150 words maximum) is required. Suggestions on the preparation of abstracts will be sent by the publisher on request.

Illustrations.—A reasonable number of halftone illustrations will be reproduced free of cost to the author, but special arrangements must be made with the editor for color plates, elaborate tables, or extra illustrations. To insure clear reproduction, all copy for zinc cuts, including pen drawings and charts, must be prepared with India ink, and a black ribbon must be used for typewritten material. Only good photographic prints and original drawings should be supplied for halftone work.

Exchanges.—Contributions, letters, exchanges, reprints, and all other communications relating to the Journal should be sent to Dr. Jonathan C. Meakins, 3640 University Street, Montreal 2, P.Q., Canada. Writers on subjects which are related in any way to cardiovascular disease are requested to place this address on their permanent reprint mailing lists.

Reprints.—Reprints of articles published among "Original Communications" must be ordered specifically, in separate communication to the publishers, The C. V. Mosby Co., 3207 Washington Blvd., St. Louis 3, Mo., U. S. A., who will quote prices upon publication of the article. Individual reprints of an article must be obtained through the author.

Review of Books.—Publishers and authors are informed that the space of the Journal is so fully occupied by matter pertaining to the branches to which it is devoted that only works treating of these subjects can be noticed. Books and monographs on the anatomy, physiology, pharmacology, therapeutics, and pathology of the heart, blood vessels, and circulation, will be reviewed when space is available. Send books to the Editor, Dr. Jonathan C. Meakins, 3640 University Street, Montreal 2, P.Q., Canada.

BUSINESS COMMUNICATIONS

Business Communications.—All communications in regard to advertising, subscriptions, change of address, etc., should be addressed to the publishers.

Subscription Rates.—For service within the United States, its possessions, and the Pan-American Postal Union countries (includes Spain), $12.00 a year; Canada, $12.50; other countries, $13.50. Students, interns, and residents are served at one-half these rates. Remittances for subscriptions should be made by check, draft, post office or express money order, payable to this Journal.

Single-Copy Prices.—To be mailed to the United States, its possessions, the Pan-American countries, and Canada, $1.25 a copy; to other countries, $1.50.

Publication Order.—This Journal is published monthly. The monthly issues form two semiannual volumes; the volume index is in the last issue of the volume—in the June and December issues.

Change of Address Notice.—Six weeks' notice is required to effect a change of address. Kindly give the exact name under which a subscription is entered, and the full form of both old and new address, including the post office zone number.

Advertisements.—Only articles of known scientific value will be given space. Forms close first day of month preceding date of issue. Advertising rates and page sizes on application.

Bound Volumes.—The Publishers Authorized Binding Service, 308 West Randolph Street, Chicago 6, Illinois, will quote prices for binding completed volumes in permanent buckram.

A red-nosed Fokker slowly spun to earth

AT 4:35 P.M., on October 30, 1918, a lone Spad biplane, marked with the symbol of the "Hat-in-the-Ring" Squadron, hawked down through the quiet skies over Grande Pré. Seconds later, a twenty-round burst of its guns smashed full into the center of a low-flying Fokker and sent the German plane swirling earthward like an autumn leaf.

The squadron C.O., Captain Eddie Rickenbacker, had downed his last enemy plane of the war, setting a record for aerial combat never equaled: 26 victories in 7 months. It made him the American ace of aces.

A year earlier, his mother had written, "fly slowly and close to the ground"; but it was advice that Eddie Rickenbacker—like many of his fellow Americans—has never been able to take. His calculating courage, ingenuity and drive are typical of our greatest asset.

Which is not simply factories, farms, or gold—but millions of a particular kind of people called Americans. And it is these people—people like yourself—who stand behind what is probably the world's finest investment: U. S. Series E Savings Bonds.

To buy these Bonds is to join them in their proud confidence of their country and its future—and to protect your own personal security as well.

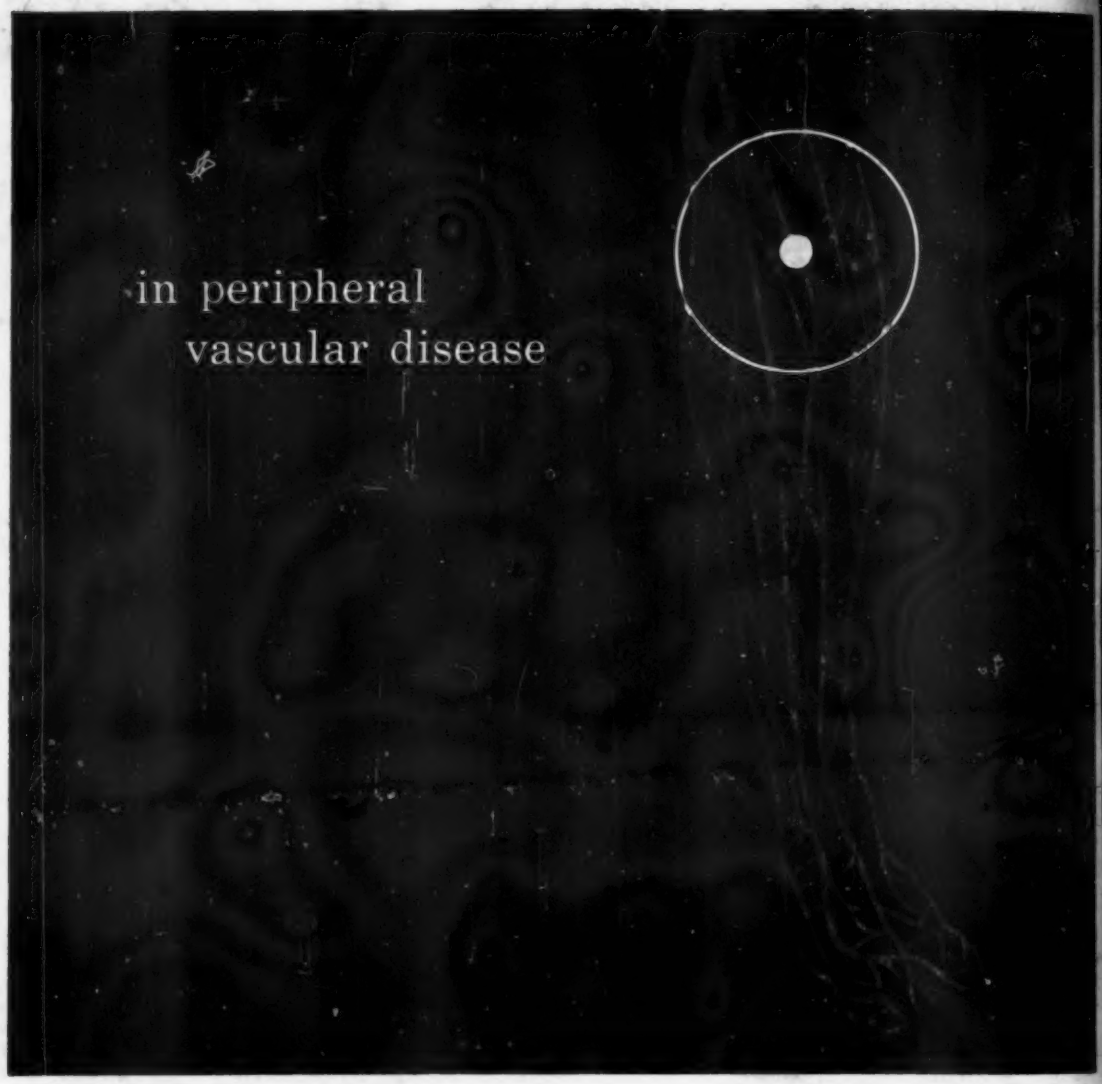
It's actually easy to save money—when you buy United States Series E Savings Bonds through the automatic Payroll Savings Plan where you work! You just sign an application at your pay office; after that your saving is done *for* you. And the Bonds you receive will pay you interest at the rate of 3% per year, compounded semiannually, for as long as 19 years and 8 months if you wish! Sign up today! Or, if you're self-employed, invest in Bonds regularly where you bank. There's no surer place to put your money, for United States Savings Bonds are as safe as America!

Safe as America—
U.S. Savings Bonds

The U.S. Government does not pay for this advertisement. It is donated by this publication in cooperation with the Advertising Council and the Magazine Publishers of America.

INDEX TO ADVERTISERS

Please mention "American Heart Journal" when writing to our advertisers—It identifies you



'Paveril Phosphate'

(DIOXYLINE PHOSPHATE, LILLY)

. . . relaxes vasospasm

When occlusion initiates a reflex spasm in the neighboring vessels, 'Paveril Phosphate,' by direct action on smooth muscle, relieves vasospasm and induces local vasodilation. Blood flow is increased, and collateral circulation is encouraged. This permits more rapid rehabilitation of the limb.

SUPPLIED AS: Tablets of 1 1/2 and 3 grains.

DOSE: 3 grains three or four times daily, up to 30 grains in twenty-four hours.

Lilly

QUALITY / RESEARCH / INTEGRITY

ELI LILLY AND COMPANY • INDIANAPOLIS 6, INDIANA, U.S.A.